Long-Term Risk Factors for, and the Impact of Age-related Muscle Loss on the Musculoskeletal Health of Older Adults

by

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The following thesis includes work which has been submitted for publication in peer-reviewed journals. Publication details for each Chapter are described in the "Publications arising from the thesis" section. Proportionate co-author contributions were as follows:

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Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

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Abstract

Loss of skeletal muscle mass and function with ageing is a major public health concern with substantial financial implications. This thesis aims to examine the risk factors for age-related muscle changes over 10 years and the impact that these changes have on falls risk, fracture, mortality, and health-related quality of life (HRQoL) in community-dwelling older adults.

Data from a population-based sample of older adults aged 50–80 years (51% women; mean age 63±7.4 years) studied at baseline, 2.5, 5, and 10 years were analysed. Appendicular lean mass (ALM) and bone mineral density (BMD) were assessed by Dual-energy X-ray Absorptiometry (DXA). Handgrip strength (HGS) and lower-limb muscle strength (LMS) were measured using dynamometer, and muscle quality was calculated (muscle strength/muscle mass). Physical activity [steps/day] was assessed using a pedometer and the intensity of physical activity was measured using an accelerometer. Falls risk was measured using the Physiological Profile Assessment, fractures were self-reported and mortality was ascertained from the death registry. Serum 25-hydroxyvitamin D [25(OH)D] was assessed by radioimmunoassay, and HRQoL, knee pain and dysfunction were assessed using standardised questionnaires.

Traditionally, analysis has focused on examining how loss of muscle mass, strength and muscle quality differ between individuals (between-person comparison). Less well recognised is how variability in risk factors over time within the same individual (within-person comparison) are associated with muscle loss. The first study of this thesis described the longitudinal associations of between-person and a dynamic within-person variability in serum 25(OH)D, physical activity and knee pain and

dysfunction with muscle mass, strength and muscle quality over 10 years. Both between-person and within-person increases in physical activity were associated with a higher muscle mass, strength and muscle quality. Within-person and between-person increases in knee pain and dysfunction were associated with a lower muscle strength and quality but not muscle mass. Between-person effects showed that higher average 25(OH)D was associated with higher 10-year average muscle mass, strength and muscle quality; whereas, within person increases in 25(OH)D was associated with a higher muscle strength and quality but not muscle mass.

The second study compared the performance of low muscle mass, muscle strength and muscle quality assessed at baseline with falls risk, incident fracture and mortality over 10 years. All baseline muscle strength and muscle quality measures were significantly associated with higher falls risk score at 10 years. Low handgrip and ALM/body mass index (BMI) were the only significant predictors of fracture and mortality respectively.

The third study described the longitudinal association of between-person and within-person variability in serum 25(OH)D, physical activity, knee pain and dysfunction with falls risk over 10 years. Knee pain and dysfunction above an individual's usual level of pain increases the risk of falling, whereas, increasing one's own moderate-to-vigorous physical activity level further reduced their risk of falling. Between-person but not within-person associations were observed between 25(OH)D and falls risk.

The fourth study examined the associations between low muscle mass, upper- and lower-limb muscle strength with HRQoL over 10 years. Participants with low LMS and low HGS (in women only) at baseline had a clinically meaningful difference in

10-year HRQoL compared to those with normal strength. There was a weaker but still significant association between low muscle mass and 10-year HRQoL.

The final study described the relationship between low muscle mass or strength, in the presence of osteopenia, with fracture and mortality risk. Incident fracture risk was significantly higher in participants with both osteopenia and dynapenia (osteodynapenia) compared to those without dynapenia or osteopenia. Mortality risk was significantly higher in participants with both osteopenia and sarcopenia (osteosarcopenia) compared to those without sarcopenia or osteopenia. However, osteosarcopenia and osteodynapenia did not lead to a significantly greater fracture or mortality risk compared to having these conditions on their own.

In conclusions, in addition to traditional between-person associations, variability in physical activity, 25(OH)D, knee pain and dysfunction within an individual over time relate to muscle changes and falls risk. Within-person effects were generally weaker compared to between-person estimates. Furthermore, muscle strength, which can be easily measured in clinical practice, appears more important than muscle mass for identifying individuals with a higher falls risk, fractures and poorer quality of life. However, muscle mass appears to be a better predictor of mortality risk. Low BMD combined with low muscle mass or strength does not significantly increase the risk of fracture or mortality compared to having low BMD or low muscle mass/strength alone, suggesting that combined assessments may not add additional risk for fracture and mortality.

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Publications Arising from the Thesis

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Scientific Presentations Arising from the Thesis

Oral presentations

July, 2017 International Association of Gerontology and Geriatrics World Congress, San Francisco, United States.

'Between-Person and Within-Person Variability in Vitamin D, Physical Activity, Pain, and Falls Risk'

April, 2017 15th World Congress on Public Health, Melbourne, Australia

'Longitudinal Associations Between Serum 25-Hydroxyvitamin-D Physical Activity And Knee Pain And Dysfunction With Muscle Mass, Strength And Quality In Community-Dwelling Older Adults'

November, 2016 7th Biennial Conference of the Australian and New Zealand Falls Prevention Society, Melbourne, Australia

'Between-Person and Within-Person Variability in serum 25-hydroxyvitamin D, Physical Activity, Knee Pain and Falls Risk.'

November, 2016 First Australian and New Zealand Conference on Sarcopenia and Frailty, Melbourne, Australia

'Prospective Associations of Low Muscle Mass and Function with 10-year Falls Risk, Incident Fracture and Mortality in Community-dwelling Older Adults'

September, 2016 Australasian Epidemiology Association 23rd annual Scientific Meeting, Canberra, Australia

'Association of Between-Person and Within-Person Variability in serum 25-hydroxyvitamin D, Physical Activity, Knee Pain and Dysfunction and Falls Risk in Community-dwelling Older Adults.'

December, 2015 Emerging Researchers in Ageing Conference, Parkville, Melbourne, Australia

'Does muscle strength mediate the association between vitamin-D, physical activity, knee pain and dysfunction and falls risk in older people?

November, 2015 Australian New Zealand Bone and Mineral Research Annual Scientific Meeting 2015, Hobart, Tasmania,

'Does muscle strength mediate the association between 25–hydroxyvitamin D, physical activity, knee pain and dysfunction and falls risk in older people: Findings from the Tasmanian Older Adults Study?

September, 2015 Population Health Congress, Hotel Grand Chancellor, Hobart, Tasmania

'Examining falls risk over 10 years: Findings from the Tasmanian Older Adults Cohort Study'

Poster presentations

March, 2017 World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal diseases Florence, Italy

'Longitudinal Associations Between Serum 25-Hydroxyvitamin-D Physical Activity And Knee Pain And Dysfunction With Muscle Mass, Strength And Quality In Community-Dwelling Older Adults'

March, 2017 World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal diseases Florence, Italy

'Prospective Associations of Low Muscle Mass And Strength With 10-Year Health-Related Quality of Life In Community-Dwelling Older Adults'

March, 2017 World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal diseases

Florence, Italy

'Longitudinal Associations Between Serum 25-Hydroxyvitamin-D Physical Activity And Knee Pain And Dysfunction With Muscle Mass, Strength And Quality In Community-Dwelling Older Adults'

Awards Resulting from the Thesis

June, 2017	Australian and New Zealand Bone and Mineral Society Travel Grant, 2017
March, 2017	Young Investigator Award for contributions to the field of bone and mineral research. Award presented by the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO).
November, 2016	Award for the best oral presentation at the first Australian and New Zealand Conference on Sarcopenia and Frailty.
November, 2016	The most outstanding Abstract (Clinical Sciences), at the first Australian and New Zealand Conference on Sarcopenia and Frailty.
September, 2016	Australasian Epidemiology Association (AEA) Student Award for submitting exemplary abstract to the AEA conference.
December, 2015	Emerging Researcher in Ageing Travel Award
September, 2015	Australasian Epidemiology Association (AEA) Student Award for submitting exemplary abstract to the Population Health Congress.
November, 2014	Tasmanian Graduate Research Scholarship, 2014

List of Abbreviations

25(OH)D	25-hydroxyvitamin D
ADLs	Activities of daily living
AFM	Appendicular fat mass
ALM	Appendicular lean mass
ALMBMI	Appendicular lean mass divided by body mass index
ALMHH	Appendicular lean mass divided by height squared
ALMR	Residual of the regression of ALM on height and total body fat mass
ALMW	Appendicular lean mass divided by weight
AQoL	Assessment of quality of life instrument
BMD	Bone Mineral Density
BMI	Body mass index
CI	Confidence interval
DXA	Dual-energy x-ray absorptiometry
Health ABC	Health, Aging and Body Composition study
HGS	Handgrip strength
HRQoL	Health-related quality of life
ICC	Intra-class correlation
IL-	Interleukin-
Kg	Kilogram
KJ	Kilojoule
LASA	Longitudinal Aging Study Amsterdam
LLM	Lower-limb muscle mass
LMS	Lower-limb muscle strength

LMQ	Leg muscle quality
MPB	Muscle Protein Breakdown
MPS	Muscle Protein Synthesis
MRI	Magnetic resonance imaging
MVPA	Moderate-to-vigorous physical activity
OA	Osteoarthritis
PA	Physical activity
PPA	Physiological profile assessment
PSI	Pounds per Square Inch
QoL	Quality of life
RR	Relative risk
SD	Standard deviation
TASOAC	Tasmanian Older Adult Cohort study
TLR4	Toll-like receptor 4
UK	United Kingdom
US	United States
UMQ	Upper-limb muscle quality
WOMAC	Western Ontario McMasters Osteoarthritis Index

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Chapter 1: Introduction

1.1 Background

The global population is ageing and this is due to an increase in life expectancy and a decline in fertility [1]. In Australia, the number of older people is projected to increase from 3.8 million in 2016 to 6.3 million in 2036 [2]. Ageing is characterised by a decline in physiological function and an increase in chronic musculoskeletal conditions such as osteoporosis, osteoarthritis and rheumatoid arthritis [3]. Therefore, promoting a healthy and high quality of life among the growing proportion of older people is a major public health priority. Loss of muscle mass with ageing is perhaps the most dramatic decline in structure and function [4]. These changes have a detrimental impact on multiple health outcomes in older people and could substantially increase healthcare costs [5, 6]. Although there are currently no direct cost estimates attributed to the health consequences of muscle loss in Australia, the financial implication is likely to be substantial [7]. The most recent estimates from the United States show that direct costs attributable to muscle loss with ageing (sarcopenia) was 18.5 billion in 2000, accounting for 1.5% of the total healthcare expenditure at that time [5]. Studies from European countries also show that irrespective of the underlying medical condition, low muscle mass or strength at hospital admission independently increases hospital costs by 34% or more [8, 9].

Despite the health and financial implications of sarcopenia, limited long-term prospective studies have examined the risk factors for, and the impact of muscle changes on health outcomes such as falls, fracture and mortality among community-dwelling older adults. Longer-term studies are crucial as it would broaden our understanding of changes in skeletal muscle and may help predict and identify

individuals at risk of greater muscle loss over a long-term period. Furthermore, such studies may also help in the design of interventions aimed at minimising muscle loss. Therefore, this thesis aims to examine the risk factors for age-related muscle changes over 10 years and the impact that these changes have on falls risk, fracture, mortality, and health-related quality of life (HRQoL) in community-dwelling older adults.

1.2 Age-Related Skeletal Muscle Loss: Assessments and Diagnostic Criteria

Muscle loss with ageing received considerable research attention when, in 1989, Irwin Rosenberg first used the word 'sarcopenia' (Greek 'sarx' or flesh + 'penia' or loss) to describe the age-related decline in lean muscle mass [10]. Since then there has been substantial research into the association between sarcopenia and various health outcomes in older people. For instance, a search in Medline (1990 – 2016) yielded 19 studies in 1995, 39 studies in 2000 and 903 in 2016.

Muscle mass and strength increase in the early years of life until about 30 years after which there is a progressive decline, resulting in the loss of 20 – 40% of muscle mass and strength by the seventh and eighth decade of life in both men and women (Figure 1.1) [11, 12]. The loss of muscle mass with ageing has been attributed to a reduction in the size and number of type 1 (slow-twitch) and type 2 (fast-twitch) muscle fibres [11, 13]. However, a more recent study showed that smaller fibre size, particularly type 2 muscle fibres largely explained the differences in the muscle mass of young (mean age ±SD: 23 ± 1 year) and older people (mean age ±SD: 71 ± 1years) [14].

This finding suggests that reduced muscle mass with ageing may be mainly attributed to a reduction in size rather than a loss in the number of muscle fibres [14].

The loss of muscle mass is associated with a concomitant fat infiltration (myosteatosis) [Figure 1.2]. Fat infiltration within and around skeletal muscle impairs the physiological function of the muscle and it is associated with reduced muscle function and poor physical performance [15-17]. An area of contention is whether age-related muscle loss is a pathological or biological process, in part because of the progressive decline in muscle mass and function even in relatively healthy older adults [11]. Terminologies such as 'secondary sarcopenia', 'myopenia' and 'muscle-wasting disease' have been proposed to distinguish decline in muscle mass or strength associated with a known aetiology from 'primary sarcopenia' which is solely due to ageing [18-20]. Given the increase in co-morbidities with age, distinguishing between primary and secondary sarcopenia may be challenging [21]. Indeed, chronic conditions such as diabetes, obesity, and hyperthyroidism would accelerate the loss of muscle mass and strength [22, 23].

In the last decade there has been extensive efforts to identify the threshold with which loss of muscle mass and function becomes clinically relevant [24, 25]. An important advancement in this regard is some level of convergence in the proposed diagnostic criteria for sarcopenia [26], leading to the recognition of sarcopenia with the code M62.84 in the International Classification of Diseases, tenth revision, clinical modification (ICD-10-CM) [27]. An implication of this is that sarcopenia can now be diagnosed as a disease state.

Table 1.1 outlines the numerous proposed diagnostic criteria for sarcopenia. The earliest diagnostic criteria proposed by Baumgartner and colleagues only included muscle mass [28]. The authors defined low muscle mass as appendicular lean mass (ALM) divided by height squared (HH) of two standard deviations below the mean values found in healthy young adults [28]. However, subsequent definitions incorporated a decline in muscle function (low muscle strength or physical performance). Depending on the operational definitions considered, the prevalence of sarcopenia among older adults in Australia ranges from 0% to 45.5% [29, 30]. Nonetheless, the proportion of older people with sarcopenia increases with age, irrespective of the operational definitions considered [29, 31].

Men typically have a higher muscle mass compared to women (Figure 1.3). Hence, the cut-points for sarcopenia are sex-specific in order to capture the differences between men and women [32, 33]. Besides, men experience a greater age-related decline in skeletal muscle mass compared to women, although the mechanism underlying the greater loss of muscle in men is not entirely clear [34]. Hormonal factors such as growth hormone, testosterone and insulin-like growth factors have been postulated as possible contributing factors to higher muscle loss in men [34].

Cut-points have been developed to classify older adults as having clinically relevant low muscle mass and function using reference data from young populations. Due to the ethnic and geographic variations in anthropometric measures, reference data from young adults should be of the same ethnic background as the older adults [35]. In the absence of appropriate reference data for our older Australian adult cohort, the older adults studied in this thesis were classified as having low muscle mass and function

based on the lowest quintile of the sex-specific distribution of muscle mass or strength measures [36]. This is another validated method to define clinically relevant low muscle mass and function [36, 37]

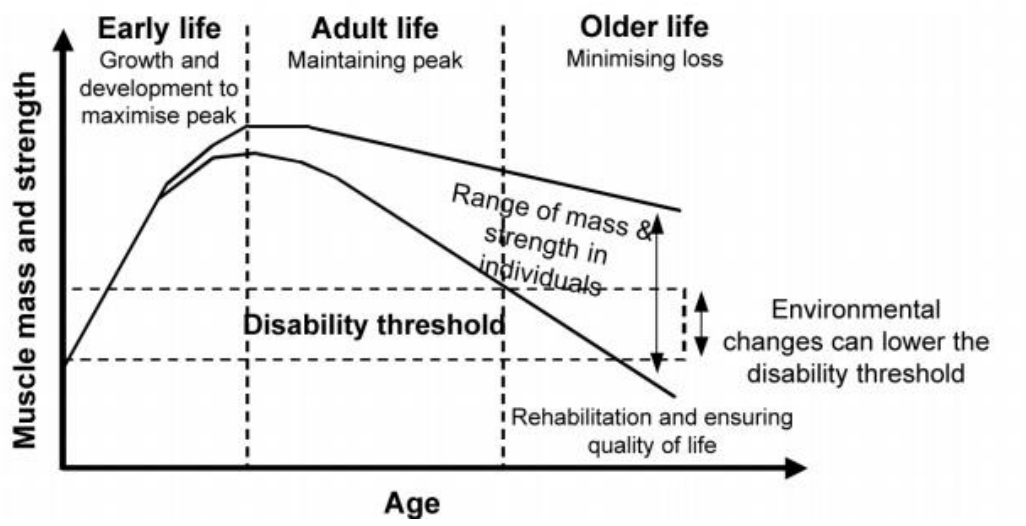


Figure 1.1 Loss of muscle mass and strength over the life course [12]

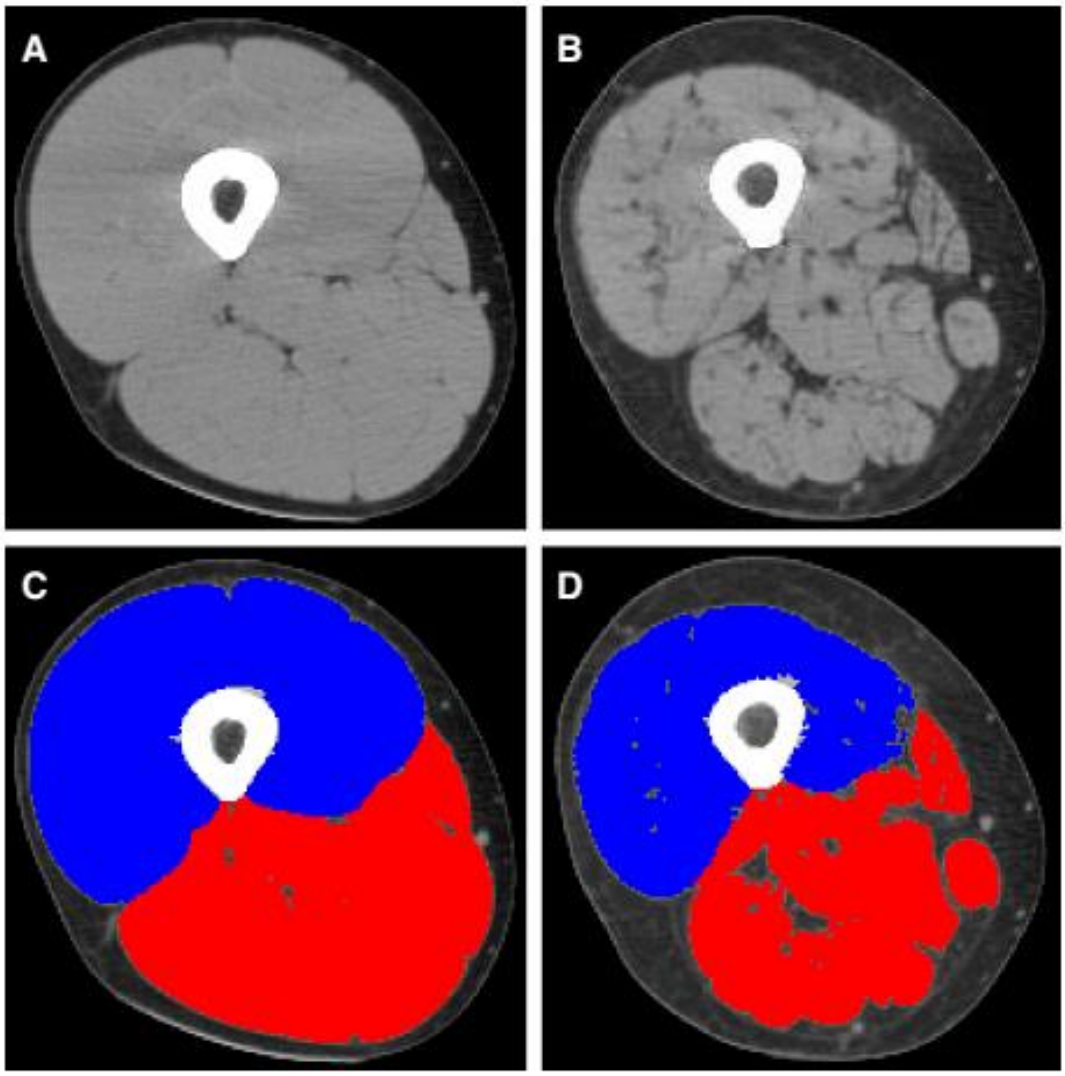


Figure 1.2 Images of CT scans of the mid-thigh of a young (A) and older adult (B). Quadriceps (blue) and whole thigh muscle area (blue and red) in the young (C) and older adult (D) are illustrated[14].

1.2.1 Limitation of some of the proposed definitions of sarcopenia

The first diagnostic criteria proposed by Baumgartner and colleagues has received wide acceptance as a valid measure of muscle mass. However, because height decreases with advancing age, ALM/HH may not be suitable for determining the changes in the prevalence of sarcopenia as it could result in an artifactual increase in the proportion of individuals with sarcopenia [38, 39]. For instance, an artifactual increase of 2.6kg/m^2 in BMI, a similar measure to ALM/HH (substitute weight for ALM) has been documented for women aged 80 years [39]. A similar increase of 1.4kg/m^2 was observed in men of the same age [39]. Furthermore, ALM/HH classified fewer obese or overweight individuals as having sarcopenia [36]. For example, in the Health Aging and Body Composition (Health ABC) Study, no participant was identified as having sarcopenia using the ALM/HH criteria [36]. In contrast, the prevalence of sarcopenia ranges from 11.5% (in men) to 21.0% (in women) when sarcopenia was defined as the residual of the regression of ALM on height and body fat mass [36]. ALM/HH was also found to underestimate the prevalence of sarcopenia among obese women in the São Paulo Ageing and Health Study (SPAH) [40]. Obese or overweight individuals with both high lean mass and fat mass may not be classified as having sarcopenia by ALM/HH criteria even though these individuals have muscle mass that is inadequate for their size and their physical performance [36].

More recently, the Foundation for National Institute of Health (FNIH) Sarcopenia Project recommends ALM normalised to BMI as a measure of low lean mass [41]. The FNIH Sarcopenia Project asserts that low muscle mass is of importance only

when it is associated with a clinically relevant functional state. Consequently, the cut-points for ALM/BMI that identify individuals with clinically relevant weakness were derived based on the presence of mobility impairment (gait speed of ≤0.8m/s) [41]. Prior studies suggest that ALM/BMI but not ALM/HH was more closely associated with poor health outcomes including mobility limitation and metabolic syndrome [42, 43]. However, because ALM/BMI is closely related to higher adiposity, it is possible that the association between ALM/BMI and poor health outcomes in older people may be related to obesity rather than low lean mass. Due to the increase in fat mass with age, individuals could still maintain or increase their total body weight. However, relative muscle mass (lean mass/weight) proposed by Janssen et al can be seen to decline with age [44].

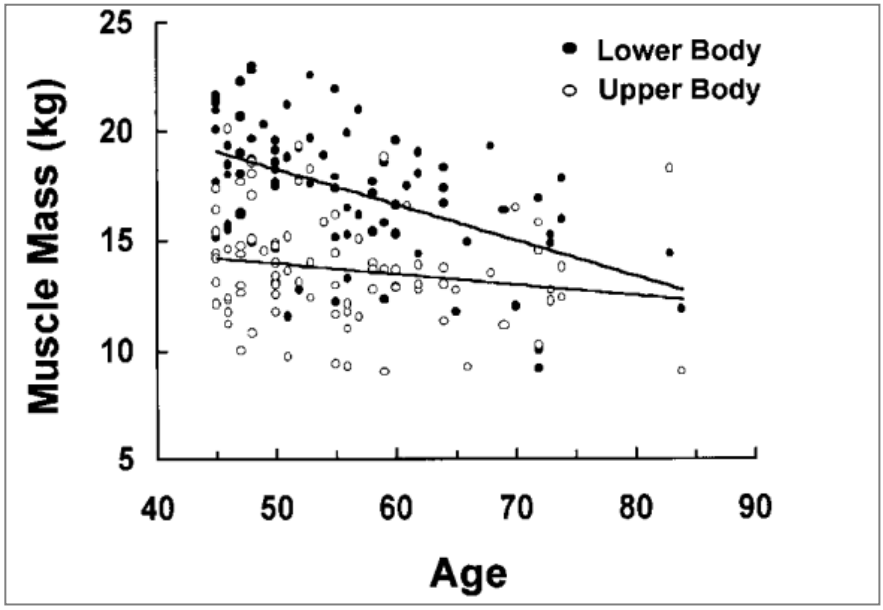
Another limitation of the proposed definitions of sarcopenia is the measurement error introduced by DXA [45]. DXA is a commonly used tool to measure ALM, however, the inability of DXA to distinguish fat infiltration within the skeletal muscle can inflate muscle mass by one to eight percent [46]. This measurement error can result in the misclassification of an individual as sarcopenic [45]. The magnetic resonance imaging (MRI) is an advance imaging technique that can distinguish intramuscular fat infiltration. Nevertheless, MRI is expensive and often inaccessible [45]. Reassuringly, a strong correlation (>0.94) has been reported between MRI and DXA measures of muscle mass, suggesting that the error in the misclassification of an individual as sarcopenic is likely to be minimal [45-47].

Table 1.1 Proposed diagnostic criteria for sarcopenia

Reference	Low muscle mass	Low muscle strength	Poor physical performance
Baumgartner criteria [28]	ALM/height^2 > 2 SD below young healthy mean	–	–
European Society for Clinical Nutrition and Metabolism Special Interest Groups (ESPEN-SIG) [48]	Percentage of muscle mass ≥2 SD below mean in young adults of the same sex and ethnic background (individuals aged 18–39 years in the NHANES III cohort)	–	Gait speed: <0.8 m/s or reduced performance in any functional test used for comprehensive geriatric assessment
European Working Group on Sarcopenia in Older People (EWGSOP) [20]	ALM/height^2 Men: ≤7.23 kg/m^2 Women: ≤5.67 kg/m^2	Handgrip strength OR Men: <30 kg; Women: <20 kg AND	Gait speed: <0.8 m/s
International Working Group on Sarcopenia (IWGS) [49]	ALM/height^2 Men: ≤7.23 kg/m^2 Women: ≤5.67 kg/m^2	–	Gait speed: <1.0 m/s
Society of Sarcopenia, Cachexia and Wasting Disorders [50]	ALM/height2 > of 2 SD below the mean of healthy persons aged 20–30 years of the same ethnic group	–	Gait speed: ≤1.0 m/s or walking distance < 400 m during a 6-min walk
Foundation of NIH Sarcopenia Project [51]	ALM/BMI Men: <0.789 Women: <0.512	Handgrip strength Men: <26 kg Women: <16 kg AND	– Gait speed: ≤0.8 m/s
Delmonico et al [37]	Sex-specific lowest 20% of the distribution of ALM/height^2		
Newman et al [36]	Sex-specific lowest 20% of the distribution of the residuals of linear regression of ALM on height and fat mass		
Janssen et al [44]	ALM/W×100 1– 2 SD below reference population is class I sarcopenia >2 SD below reference population is class II Sarcopenia		

ALM/ht^2 = ratio of appendicular lean mass over height squared; ALM/BMI = ratio of appendicular lean mass to body mass index; SD standard deviation

A



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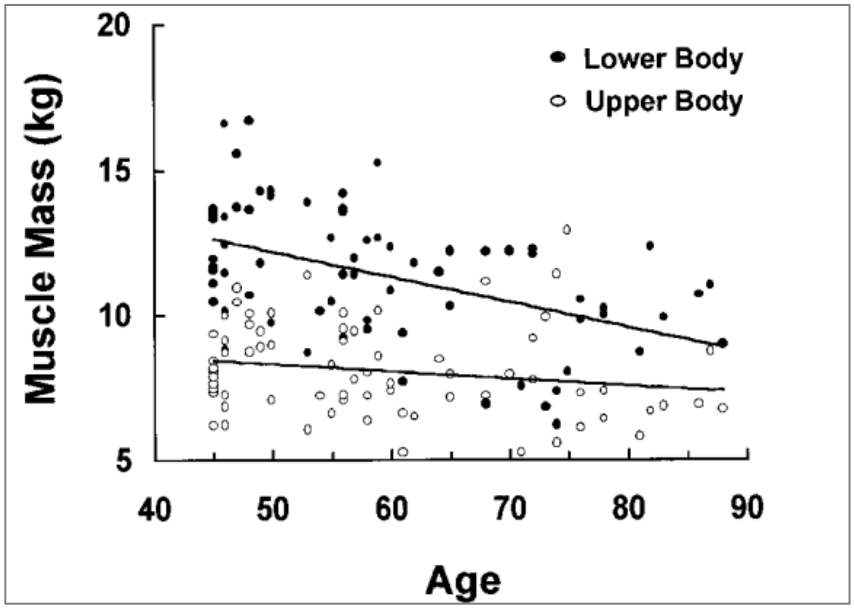

Figure 1.3 Age-related decline in upper and lower body skeletal muscle mass for men (A) and women (B) [34]

1.2.2 Discordance between age-related decline in muscle mass and muscle strength

Historically, declines in muscle strength with age has been largely attributed to the loss of muscle mass [11, 33]. However, recent studies suggest that, although both muscle mass and strength decrease with age, the two processes involve different pathophysiological processes and declines in muscle mass explain less than five percent of the variance in the loss of muscle strength [52]. After 6 weeks of resistance exercise training in one of the upper-limbs (trained arm), there was 7% increase in the strength of the untrained contralateral upper limb suggesting that changes in muscle strength are partly influenced by neural control [53, 54]. Besides, substantial loss of muscle strength may or may not be accompanied by significant loss of muscle mass, demonstrating that muscle strength (characterised by reduced muscle activation) is mostly affected in the early period of immobilisation [55, 56]. Muscle mass is a reflection of the total number of sarcomeres present in a muscle, whereas, the amount of force produced by each sarcomere together with the quality of this contractile protein and connective tissue determines the strength of the muscle [30, 32]. Hence, preserving muscle mass may not necessarily result in maintenance of muscle strength as the quality but not the quantity of sarcomeres determines muscle strength [30, 52, 57].

Indeed both muscle mass and strength decline with age, however, muscle strength declines at a faster rate than muscle mass [33, 58]. For instance, in the Health ABC study, the rate of muscle strength loss was 3.6% in men and 2.8% in women compared to 1% decline in muscle mass (for both men and women) [57]. Although

age-associated loss of muscle strength was higher compared to muscle mass, discrepancies also exist in the decline in muscle mass and strength within different regions of the body [34, 59]. For instance, the size of the quadriceps femoris muscle declines more rapidly with age compared to the biceps, anterior tibial or forearm flexor muscles (Figure 1.4) [60]. Generally, for both men and women, the rate of muscle loss in the lower-limbs is twice the rate of decline seen in the upper-limbs [34]. Although the mechanism underlying this discrepancy is not entirely clear, the decrease in mobility-related physical activity with advancing age is likely to contribute to a greater decline in lower-limb muscle [34]. However, whether the discrepancy in the decline of upper- and lower-limb muscle have a differing impact on the health of older people is not entirely clear. The long-term impact of upper and lower-limb muscle strength on falls risk, fracture, mortality (Chapter 5) and health-related quality of life (Chapter 7) are discussed in subsequent chapters.

The term ‘dynapenia’ has been proposed to distinguish loss of muscle strength from mass and to facilitate research into the mechanism underpinning age-associated decline in muscle strength [61]. However, ‘dynapenia’ has not achieved widespread usage like sarcopenia; in part, because the use of two nomenclatures to describe such a closely related concept may create some confusion [20]. Sarcopenia is commonly used to describe decline in both muscle mass and strength [20]. Nevertheless, because of the discordance between muscle mass and strength, declines in muscle mass and strength could have a differing impact on health outcomes in older people. Many but not all of the previous studies have provided evidence for the superiority of muscle strength in predicting health outcomes such as poor mobility, physical disability, hospitalisation and mortality risk over 6 years [62-64].

In addition to the loss of muscle mass and strength, muscle quality, a measure of functional properties of the muscle also reduces with age [65, 66]. Underpinning the decline in muscle quality is the increase in fat infiltration and reduction in neural activation and muscle aerobic capacity [66]. There is currently no consensus definition for muscle quality, however, it is typically defined as muscle strength per unit of muscle mass [65].

Limited long-term prospective studies have compared the association of muscle mass, strength and muscle quality with important health outcomes such as falls, fracture and mortality in community-dwelling older people. Understanding these associations is crucial in identifying the most valid clinically relevant indicators of age-related muscle loss and may also help in the design of intervention trials. The comparison of the association between low muscle mass, strength and muscle quality with falls risk, fracture and mortality over 10 years is discussed in Chapter 5 of the thesis.

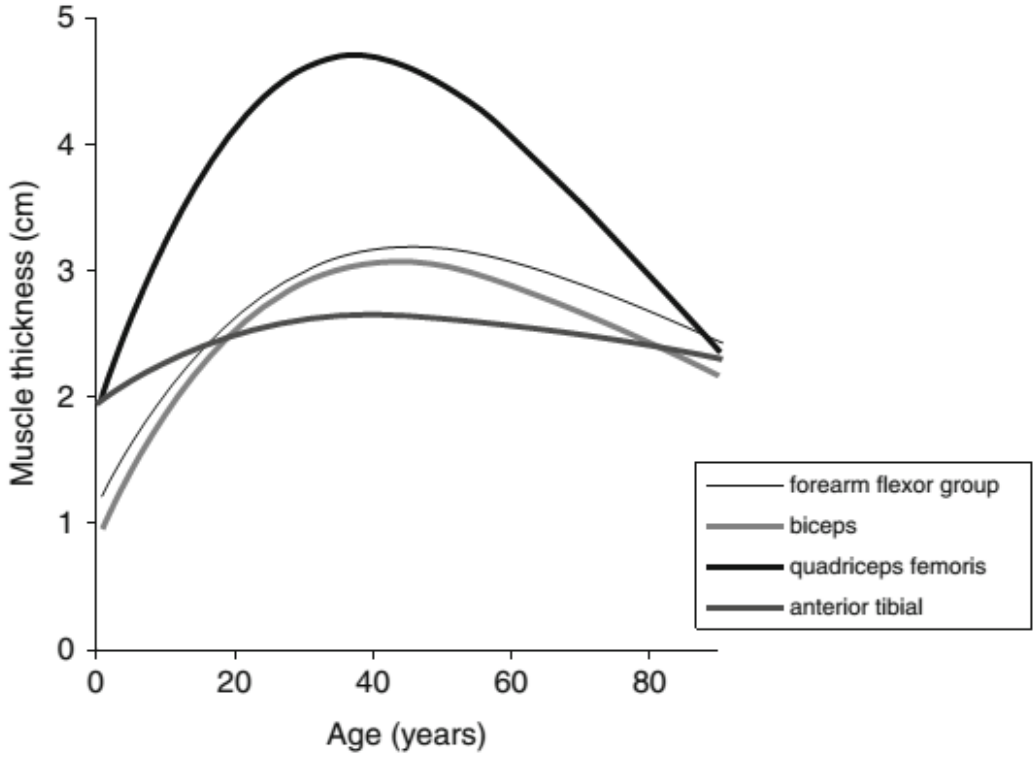

Figure 1.4 Age-related muscle changes (muscle thickness) for the biceps brachii, forearm flexor, quadriceps, and anterior tibial muscles [60].

1.3 Risk factors for age-related muscle loss: Interindividual (between-person) versus intraindividual (within-person) processes

The mechanism underlying the loss of skeletal muscle mass and strength is not entirely clear but is likely to be multi-factorial. Several modifiable risks including poor nutrition (particularly protein intake) [67], low levels of physical activity [68], low vitamin D [69], higher knee pain [70] as well as non-modifiable risk factor such as genetic makeup have been proposed [12, 32]. Non-modifiable risk factors (such as genetic makeup and ethnic background) do not change over time. Hence, these variables are referred to as time-invariant predictor variables and they contribute primarily to interindividual (between-person) differences in muscle loss. However, modifiable risk factors such as protein intake and physical activity participation change over time. Hence, these variables are referred to as time-varying predictor variables and they contribute to both interindividual (between-person) and intraindividual (within-person) differences in muscle loss. For example, physical activity differs between different individuals (between-person differences) and it also varies from time to time within the same individual (within-person variability). Previous studies have only examined between-person differences in risk factors for muscle loss [68, 71, 72]. There are no published studies describing within-person variability in risk factors for muscle loss. This is important to investigate because the inferences we make from the between-person effects (for example the magnitude and direction of effects) may not align with those we would make from the within-person effects [73].

For instance, among 245 older people undergoing post-acute rehabilitation, Rodriquez et al observed a significant within-person association between pain and functional independence such that, at time-points when participants had more pain than their average level of pain, they had a significantly less functional independence at the same time (within-person effect) [74]. Interestingly, there was no significant association between persistent pain and functional independence (between-person effect). This finding demonstrates that between-person and within-person effect can lead to different conclusions, confirming the importance of examining within-person relationships. Studies describing the association of between-person differences in physical activity, vitamin D, knee pain and muscle loss are highlighted below.

1.3.1 Physical activity and age-related muscle loss

Physical inactivity is one of the most significant contributing factors to accelerated loss of skeletal muscle mass, strength and muscle quality [22]. Epidemiological studies from different ethnic groups (Korea, Japan, France, USA, China, Switzerland and Australia) consistently report an inverse association between physical activity and muscle loss, such that muscle loss is lower in older adults who engage in higher light or moderate-to-vigorous activity [68, 71, 75-80]. Inactivity, with or without hospitalisation, has been shown to compromise muscle metabolic homeostasis and contribute to substantial loss of muscle mass and function [81-83]. For example, 10 days of continuous bed rest among healthy older adults (mean age: 67 years; 50% women) resulted in the loss of 0.95kg of DXA-derived lower extremity lean mass and a 19 Nm/s decrease in isokinetic knee extension muscle strength [84]. The apparent loss of muscle mass and strength in these healthy older people demonstrates the

detrimental impact that inactivity has on muscle mass and function in older people who are hospitalised. Interestingly, the benefits of exercise on the muscle is palpable even for a short duration. For instance, three minutes of intense exercise per week performed over six weeks was associated with physiological changes including an increase in skeletal muscle oxidative capacity [85]. Taken together, these findings underscore the significance of physical activity in maintaining muscle mass and function in older people, irrespective of the duration of the activity.

Whilst physical activity–induced benefits on muscle mass and function has been well documented, the mechanisms by which physical activity prevents muscle loss are not entirely clear. Skeletal muscle responds to a prolonged period of physical inactivity by decreasing muscle protein content and muscle fibre size, particularly type II muscle fibres [82, 86]. The loss of muscle protein content is as a result of disruption in the rate of new muscle protein synthesis (MPS) and proteolysis or muscle protein breakdown (MPB) [87]. Although MPS and MPB jointly contribute to skeletal muscle atrophy, there are controversies regarding the magnitude of the contribution of each of the two processes, with some authors suggesting inactivity-induced muscle loss is caused largely by a decrease in MPS and that MPB plays a minimal role [88, 89]. Others suggested that elevated proteolysis or MPB is the dominant mechanism responsible for inactivity-induced muscle loss [82, 90]. Regardless of the mechanism, muscle loss occurs when MPB exceeds MPS and physical inactivity contributes to this process [82, 90].

In addition to disruption in skeletal muscle homeostasis, pro-inflammatory markers which have been shown to trigger muscle loss are elevated in physically inactive

older adults [81, 91]. Specifically, toll-like receptor 4 (TLR4) and interleukin-6 (IL-6) were significantly increased in healthy older adults who were on bed rest for seven consecutive days [81]. The increase in these inflammatory markers was accompanied with a 4% loss of lower-limb lean mass. This finding demonstrates the deleterious systemic effect of physical inactivity – even for a short duration of seven days – on skeletal muscle function. Physical activity participation varies over time within the same individual [92]. However, whether variability in physical activity over time within the same individual relates to muscle changes has not been previously examined. The first longitudinal study describing the relationship of within-person variability in physical activity, in addition to traditional between-person associations, with muscle mass, strength and muscle quality is presented in Chapter 4 of the thesis.

1.3.2 Nutrition (vitamin D) and age-related muscle changes

Ageing is associated with a progressive decline in food intake (anorexia of ageing), predisposing older people to inadequate nutrient intakes and energy-protein malnutrition [93]. There is increasing evidence of a relationship between poor diet, particularly protein (1.0 to 1.2 g/kg BW/day) [94], antioxidant nutrients and vitamin D [95], and loss of muscle mass and function. Dietary protein is crucial for skeletal muscle as it provides amino acids for muscle protein synthesis. Among 2066 older people (mean age: 75 years, women: 53%) followed prospectively for over three years in the Health ABC study, individuals in the lowest quintile of energy-adjusted total protein intake lost about 40% of total and appendicular lean mass compared to those in the highest quintile [96]. Furthermore, older people who consumed more protein than the recommended dietary allowance of 0.8g/kg/day had the smallest loss

of lean mass, whereas, those who consumed at or below the recommended dietary allowance experienced the most significant loss of lean muscle mass [96]. This finding suggests that the currently recommended dietary allowance of protein may not be optimal for maintaining skeletal muscle in older people [97]. This may be because dietary protein requirements are estimated principally based on nitrogen balance and not maintenance of muscle mass [96, 98, 99]. Hence, the current recommended dietary allowance of protein is sufficient for achieving nitrogen balance but may not be adequate for maintaining muscle mass in older people [96]. Consequently, daily consumption of 1.25g/kg has been suggested for preserving muscle mass in older people [96, 100, 101].

Older people engage in fewer outdoor activities compared to other age groups, limiting their opportunity for sunlight exposure, a major source of vitamin D [102]. Indeed vitamin D levels are significantly higher in older people who engage in more outdoor activities like gardening and cycling compared to those who do not [103]. This association is independent of age, BMI or comorbidity [103]. Observational studies have reported a link between low levels of vitamin-D and loss of muscle mass and strength [104, 105]. However, findings from randomised controlled trials (RCT) and meta-analyses of these trials have been inconsistent, with some showing no effects of vitamin-D supplementation in improving muscle mass or strength and others showing a benefit for muscle strength but not muscle mass [69, 106]. For instance, a meta-analysis of 30 trials testing the efficacy of vitamin-D supplementation on muscle function in older people showed that supplemental vitamin-D improved muscle strength but not DXA-derived lean mass [69]. A more recent meta-analysis reported no beneficial effect of vitamin D supplementation with

or without calcium supplements on muscle strength in community-dwelling older adults [106]. Conflicting findings from meta-analyses could be attributed, in part, to methodological differences such as discrepancy in the selection and inclusion of RCTs in the meta-analyses resulting in different patient populations, study quality, and heterogeneity between studies. The expression of vitamin D receptor in human skeletal muscle, a mediator of 25(OH)D on muscle contractility, has been shown to decline with age and it has been linked to reduced muscle mass and function in older people [107, 108]. These findings highlight that vitamin D may play a role in age-related loss of skeletal muscle mass and function. Nevertheless, there are no published studies examining whether variability in vitamin D over time within the same individual relates to muscle changes. The association of within-person and between-person variability in vitamin D with muscle mass, strength and muscle quality in community-dwelling older people is described in Chapter 4 of the thesis.

1.3.3 Chronic diseases and age-related muscle changes

Chronic conditions such as diabetes, stroke, hypertension and rheumatological diseases are more prevalent in older people and could substantially induce accelerated loss of skeletal muscle [22, 23, 109]. Pro-inflammatory cytokines such as interleukin-1 (IL–1), IL–6 and C-reactive protein which is increased in the normal ageing process are elevated in older people with chronic conditions [71, 91, 110]. These pro-inflammatory cytokines are known contributory factors to muscle loss and the greater production of these inflammatory markers in older people with chronic conditions accelerates the loss of muscle mass and function [22, 91]. For example, older people with respiratory and cardiovascular diseases such as chronic obstructive pulmonary

diseases (COPD), chronic heart failure and peripheral arterial diseases experienced muscle loss of 10 – 40% higher compared to healthy age-matched controls [22]. The greater muscle loss in these groups of older people could be attributed in part to hypoxia, suppression of protein synthesis and overproduction of pro-inflammatory cytokines [22]. Furthermore, bed rest as a result of hospitalisation could further exacerbate skeletal muscle fibre atrophy and rapid loss of muscle function in an individual with chronic diseases [86].

1.3.4 Pain and age-related muscle changes

Pain is a major clinical symptom in chronic conditions such as osteoarthritis and rheumatoid arthritis and it is one of the main reasons for primary healthcare visit [111]. Knee pain could contribute to accelerated muscle loss via a reduction in mobility [112]. However, a direct inhibition of muscle strength by knee pain is also possible. For example, in a crossover study of 18 healthy adults, experimental knee pain induced by injecting hypertonic saline into the infrapatellar fat pad was associated with 5-15% reduction in knee strength compared to the control conditions [70]. Interestingly, there was a positive correlation between the decrease in muscle strength and the intensity of the experimentally induced knee pain, suggesting a greater reduction in muscle strength at higher pain intensities. Indeed, a history of pain is an important predictive parameter of accelerated muscle loss [71]. Nevertheless, previous studies examining the association of knee pain and muscle changes focused largely on the amount of muscle loss in older people with a higher knee pain compared to those with a lower knee pain (between-person comparison). There are no published studies describing the association of variability in knee pain

over time within the same individual (within-person) with the loss of muscle mass, strength and muscle quality. Pain experience varies over time within an individual, it is crucial to understand whether variability in pain over time is associated with muscle loss. Chapter 4 of the thesis described the first longitudinal study examining the association of within-person, in addition to the traditional between-person association of knee pain and dysfunction with loss of muscle mass, strength and muscle quality.

1.3.5 Other factors contributing to age-related muscle decline

Observational studies focus largely on lifestyle and behavioural factors modifying loss of muscle mass and strength in later life [12]. However, evidence from life course epidemiology suggests that early life environmental factors and biological factors such as low birth weight influence peak muscle mass and strength attained in adulthood [12, 113-116]. Furthermore, these early life circumstances may also determine the rate of muscle loss in later life [12, 113-116]. For instance, in the Herefordshire Cohort study individuals with low birth weight and lower weight at aged one year had significantly lower handgrip strength in later life [115]. Interestingly, the relationship between birth weight and reduced muscle strength in later life remained significant after adjusting for adult characteristics such as physical activity and current social class, suggesting that early life factors have an independent effect on muscle strength. The relationship between low birth weight and muscle strength in adulthood has been replicated in studies from several countries including Finland, Canada, Guatemala, Spain, Belgium and Australia [116].

In addition to early life circumstances, genetics have also been implicated in inter-individual differences in age-related muscle loss with 45 – 90% heritability for muscle mass and 30 – 85% for muscle strength [117]. Recently, Lucassen and colleagues showed that poor sleep quality and later sleep timing were associated with low skeletal muscle mass [118]. Although the mechanism underlying this process is yet to be elucidated, this finding suggests that while physical activity is important to stimulate the muscle, adequate rest is vital in maintaining the body homeostasis.

1.4 Health implication of age-related muscle loss

Loss of skeletal muscle mass and strength with ageing has impacts on multiple health outcomes in older people, consistent with the focus of this thesis, this section summarises the relationship between age-related muscle loss and falls risk, fracture, mortality and health-related quality of life.

1.4.1 Relationship between age-related muscle loss and falls and fracture

Falls among older people are a major public health burden which can result in contusion, laceration and dislocation [119] to more severe injuries such as fracture and traumatic brain injury [120]. Falls are a leading cause of injury-related hospitalisation [121], and only about 50% of older adults admitted to hospital after a fall will survive the following year [122]. Even when falls do not result in any physical injury they are associated with social and psychological consequences [123]. These consequences may include fear of falling which further results in reduced mobility, social isolation, depression [124] and a subsequent increase in falls risk [125]. Other than the health and psychosocial impacts, the economic impact of falls is

also palpable. For instance, falls-related injuries was estimated to cost $604 million to the Australian healthcare system in 2011 [126]. By 2051 these injuries are expected to triple and estimated to cost the Australian health sector over $1.4 million annually [126]. With the growing population of older people in Australia, falls rates are likely to increase [2].

Previously identified risk factors for falls among older adults include abnormalities in gait and balance, polypharmacy, visual and cognitive impairments [125, 127]. However, muscle weakness has been identified by the joint British and American Geriatrics association as the single biggest intrinsic risk factor for falls [128, 129]. Due to the discrepancy between muscle mass and strength, there has been an increasing interest in the independent role of muscle mass and strength with falls. Examining the independent impact of muscle mass and strength on falls is crucial to determine the focus of interventions aimed at reducing falls risk. Prior studies have consistently reported an association between low muscle strength and single fall, recurrent falls as well as injurious falls [130-132]. However, evidence for muscle mass has been inconsistent with some studies showing an association between low muscles mass and falls [38, 133] while others found no evidence for a relationship between low muscle mass and falls in women [134].

Studies describing the relationship between muscle weakness and falls often measure muscle strength of either the upper (handgrip strength) or lower-limb [132]. Handgrip strength is a marker of overall muscle strength in the body and it has been shown to be an important predictor of multiple health outcomes [135, 136]. However, whether upper-limb muscle strength is a better predictor of falls is not entirely clear. In a

systematic review and meta-analysis of studies evaluating the association between muscle weakness and falls, Moreland and colleagues reported a combined odd ratio of 1.76 (95% confidence interval (CI): 1.31 – 2.37) for lower extremity muscle weakness and a lower odds ratio of 1.41 (95% CI: 1.25 – 1.59) for upper-limb muscle weakness [132]. Notably, only four studies were included in their meta-analysis for upper-limb muscle weakness compared to nine studies which examined lower-limb muscle strength. Further research is required to assess the performance of muscle mass, upper and lower-limb muscle strength with falls in the same cohort of older people. If found to be more effective, handgrip strength is a simple and inexpensive test that can be easily adopted in clinical settings to identify older people at risk of falls over a long term.

One of the major detrimental health impacts of falls is fracture [137]. A bone is fractured when the energy transmitted to it by a fall or other trauma-related activity exceeds bone strength [138]. Whether a fall results in a fracture is determined by four factors: 1) the location of the impact, determined by the direction of fall, 2) the energy generated by the fall, 3) the absorption of energy or protective response of soft tissue overlying the bone and 4) the bone strength [139]. In addition to contributing to falls, low muscle mass and both upper and lower limb muscle strength play major roles in the four factors which determine whether or not a fall would result in a fracture [138]. However, limited long-term prospective studies have compared the association of low muscle mass, upper- and lower-limb muscle strength with falls and fracture in the same group of community-dwelling older people. Such studies are crucial for two reasons. One, it would broaden our understanding of which measure of muscle loss is most clinically important in identifying older people at risk of falls and fracture over a

long-term. Secondly, findings from such a study may help in the design of long-term interventions aimed at reducing falls and fracture risk [140, 141]. The association between muscle mass, upper- and lower-limb muscle strength with falls risk and fracture over 10 years among community-dwelling older adults is examined in Chapter 5 of the thesis.

1.4.2 Other risk factors for falls

In addition to age-related muscle loss, other factors such as physical activity, vitamin D, and knee pain have also been identified as important risk factors for falls in community-dwelling older people. There is an abundance of research on between-person differences in these risk factors for falls in older people. However, limited studies have examined whether variability in physical activity, vitamin D and knee pain over time within the same individual is associated with falls risk. Studies examining the association of between-person differences in physical activity, vitamin D, knee pain and falls risk are highlighted below.

Falls risk has been shown to be consistently higher in older people with low levels of physical activity [142-145]. However, higher levels of physical activity have also been hypothesized to be associated with greater falls, in part because higher levels of physical activity increases opportunity for falls, particularly in older people with poor balance [146, 147]. Nonetheless, data from a large sample of community-dwelling older adults (N=1337) from the longitudinal Aging Study Amsterdam (LASA) reported no evidence of a non-linear relationship between physical activity and falls (*P*-value for PA^2 >0.20) [142]. The association between physical activity and falls was not modified by mobility limitations and there was no evidence for an interaction

between physical activity and poor physical performance or functional limitations, suggesting that higher levels of physical activity may not have a detrimental impact on older people with poor physical function [142]. Older people may adapt their physical activity to suit their level of physical function and a higher level of physical activity may lead to an improvement in muscle strength and a reduction in falls. Nevertheless, the association of variability in physical activity over time within the same individual with falls risk has not been previously examined.

Lower levels of vitamin D has been consistently shown to be associated with a higher falls risk in observational studies [148, 149]. However, evidence from RCTs testing the hypothesis of whether vitamin D supplementation reduces falls are inconclusive [150-152]. Recent RCTs from Australia (500,000 IU/year) and Switzerland (60,000 IU/month) showed that high dose of vitamin D supplementation increased the risk of falls [150, 151]. Notably, falls were particularly higher among older people with sufficient vitamin D at baseline [150]. It is unclear why a high dose of vitamin D supplementation increases falls in older people. However, possible reasons have been postulated. For instance, it is possible that a high dose of vitamin D may trigger a short-term protective response in which the enzyme (25-hydroxyvitamin D-24-hydroxylase [CYP24]) that catabolise 1,25(OH)D is up-regulated [153]. This may lead to lower availability of 1,25(OH)D in the blood and tissues (such as bone and muscle) potentially increasing the risk of falls [153]. Alternatively, high monthly doses of vitamin D may have some beneficial effects such as improved physical performance[154, 155], improved mood[156] and reduced pain[157] potentially leading to greater mobility and higher exposure to falls [154]. Other trials which included older people with low vitamin D at baseline found that vitamin D

supplementation reduced falls [158]. These findings suggest that vitamin D may be effective in reducing falls in older people with low vitamin D. Nonetheless, it is unclear whether variability in vitamin D over time within the same individual is associated with an increase in falls risk.

Pain is prevalent in older people and the knee joint is one of the three most frequently reported painful sites [159]. There are multiple pathways through which knee pain could lead to falls. For instance, knee pain could increase falls through muscle weakness associated with mobility disability [112]. Furthermore, psychological factors including depression, fear and anxiety associated with knee pain also predispose older people to greater risk of falls [160]. For example, pain may contribute to loss of confidence and an increase in fear of falling [161]. Fear of falling could alter gait pattern and can lead to a further increase in falls [162]. Pain experience varies over time within the same individual and this within-person variability in pain has been shown to be associated with other health outcomes such as insomnia [163]. Less is known about the relationship between within-person variability in knee pain and falls risk in older people.

The first longitudinal study describing the associations of within-person variability in knee pain, serum 25(OH)D and physical activity (in addition to between-person estimates) with falls risk in community-dwelling older adults is presented in Chapter 6 of the thesis.

1.4.3 Relationship between age-related muscle loss and health-related quality of life

Despite the widely documented impact of low muscle mass and function on health outcomes such as falls, fracture and mobility disability, there have been limited studies which have described the association between low muscle mass and strength and health-related quality of life (HRQoL). Recently, Woo et al synthesised evidence from 20 studies examining the relationship between low muscle mass and strength with HRQoL in older adults [164]. Notably, 18 of these studies were cross-sectional and only 2 were longitudinal studies with 3 – 6 years follow-up period. Findings from these studies were inconsistent with some showing an association between low muscle mass and strength and HRQoL while others reported no association [164-166]. Due to the inherent limitations associated with cross-sectional study findings, long-term longitudinal studies are warranted to clarify the relationship of low muscle mass and strength with HRQoL in older adults. Furthermore, whether upper- and lower-limb muscle strength has differing effects on HRQoL is yet to be ascertained. The prospective association between low muscle mass, low upper and lower-limb muscle strength with HRQoL over 10 years in community-dwelling older people is examined in Chapter 7 of the thesis.

1.4.4 Relationship between age-related muscle loss and mortality

Muscle weakness contributes to de-conditioning and an increased risk of mortality [63, 64, 167]. Skeletal muscle mass also plays a role in survival as it serves as the major reservoir to replenish amino acid in vital organs and tissues like the brain, liver and the heart during physiological stressed state [99]. For example, strong association

have been consistently documented between low muscle mass and length of survival in patients with acetabula fracture and among those undergoing liver transplantation and oncologic procedure [168-170]. However, whether the relationship of muscle mass with mortality is independent of muscle strength has been an area of increased research interest. In a prospective study of 2292 older adults from the Health ABC study, Newman and colleagues showed that both handgrip strength and quadriceps muscle strength were significant predictors of mortality over 6 years whereas no association was observed between DXA-accessed lean mass and mortality [64]. Furthermore, the relationship between muscle strength and mortality remained significant after adjusting for muscle mass, albeit, muscle mass slightly reduced the magnitude of the effect of muscle strength. This finding suggests that muscle strength captures more important aspects of ageing that is related to mortality. Nonetheless, whether the superiority of muscle strength in estimating mortality persists over a decade is not entirely clear. Consequently, the relationship between muscle mass, muscle quality, upper- and lower-limb muscle strength with mortality over 10 years among community-dwelling older adults is examined in Chapter 3 of this thesis.

1.5 Bone-muscle interaction and health of older people

There is increasing research interest in how low muscle mass or function and low bone mass jointly influence health and health-related quality of life of older people [134, 171]. This is important as it would not only help identify the health risk associated with the co-existence of low muscle mass/function and low bone mass but also help in the design of interventions that target two conditions simultaneously.

Muscle exerts a significant mechanical force on bones, consequently, muscle weakness is believed to lead to low bone mass [172-174]. However, the reverse is also possible, for instance, in bone disease such as osteogenesis imperfecta, there is muscle weakness even when there is no myopathy, suggesting that the interconnection between muscle and bone is beyond mechanical forces [175]. The endocrine function of both muscle and bone has been previously documented, although the role of muscle as an important endocrine/secretory organ has only been recognised in the last decade [176-178]. The endocrine function of both muscle and bone has led to the hypothesis of a biochemical communications between the two organs [175, 179]. For instance, a decline in muscle mass is associated with abnormal glucose metabolism and alterations in muscle-related proteins which directly affect bone metabolism [180, 181]. Furthermore, both bone and muscle are infiltrated by fat leading to a toxic effect on cell function and survival [182, 183]. Future studies incorporating cellular and molecular mechanisms are warranted to better understand the biochemical communication between muscle and bone. Indeed, the co-existence of low muscle mass/function and low bone mass increased the risk of falls, impaired mobility and fracture [134, 180, 184]. However, current evidence is largely from cross-sectional studies, hence, it is unclear whether findings from these cross-sectional studies track over time. The relationship between the simultaneous occurrence of low bone mineral density and low muscle mass/strength with fracture and mortality is examined in Chapter 8 of the thesis.

1.6 Summary

Increasing life expectancy in Australia is accompanied with an increase in the population of older people. The number of older people in Australia is projected to increase from 17% in 2006 to 24% in 2036. Age-related decline in skeletal muscle mass and strength is a major public health concern as it is associated with functional declines and loss of independence among older people. This has a major impact on older people, and could substantially increase healthcare expenditure. While both muscle mass and strength decline with age, muscle strength declines at a faster rate and could be more important to consider in order to identify older people at a greater risk of poor health outcomes. Discrepancy also exists in the rate of decline in muscle strength of the upper and lower-limb, with strength declining at a faster rate in the lower-limbs potentially due to the role of lower-limbs in mobility. Limited long-term prospective studies have compared the association of muscle mass, upper and lower-limb muscle strength with falls, fracture and mortality in community-dwelling older people. Physical activity, knee pain, and nutrition including serum 25(OH)D are important contributing factors to age-related muscle loss. Nonetheless, previous studies have only examined the association of between-person differences in physical activity, serum 25(OH)D and knee pain with muscle loss. There are no published studies describing the association of within-person variability in these risk factors and loss of muscle mass, strength and muscle quality. This is important to investigate because the inferences we make from the between-person effects may not align with those we would make from the within-person effects. Importantly, both estimates may lead to different conclusions. The research questions addressed in this thesis are described in the following Chapter.

Chapter 2: Research questions

The research questions addressed in the thesis are highlighted below. In a cohort of community-dwelling adults aged 50 - 80 years examined at baseline, 2.5, 5 and 10 years later:

1. What is the relationship between within-person and between-person variability in physical activity, vitamin-D, knee pain and dysfunction and muscle loss?

2. Which measure of muscle mass and function is more strongly associated with falls risk, self-reported fracture and mortality over 10 years?

3. What is the relationship between within-person and between-person variability in physical activity, vitamin-D, knee pain and dysfunction and falls risk over 10 years?

4. To what extent does low muscle mass/strength influence the health-related quality of life over 10 years?

5. Does the simultaneous occurrence of osteopenia with low muscle mass or strength significantly increase the risk of fracture and mortality than osteopenia or low muscle mass/strength alone?

Chapter 3: Methodology

3.1 Prelude

The study in this thesis was conducted as part of the Tasmanian Older Adult Cohort (TASOAC) study and a number of outcome variables, predictor variables and covariates have been used. This Chapter describes the study settings and participants of the TASOAC study. The dependent and independent variables examined in the subsequent chapters of the thesis are also described. Statistical analyses techniques are described in subsequent relevant chapters.

It should be noted that the following chapters are presented in the form in which they were submitted to, or accepted by, peer-reviewed journals for publication. Thus, throughout these chapters there are some differences in the description of methods, analyses, results, and interpretations, mainly due to requests from journal reviewers.

3.2 Study population and design

The TASOAC study is a prospective, population-based study primarily aimed at examining the causes and progression of osteoarthritis. Men and women aged 50 years and above were selected using a sex-stratified random sampling technique from the electoral roll in Southern Tasmania (population 229,000). A total of 1100 adults (response rate = 57%) consented to participate in the study. Participants were excluded if they had any implants that would prevent them from undergoing an MRI or they were living in a nursing home. Participants who consented to participate in the study were invited to attend a clinic at the Menzies Institute for Medical Research, Hobart, Tasmania between March 2002 and September, 2004. They were invited for follow–up clinic assessments at 2.5, 5, and 10 years after the initial clinic assessment.

The number of participants at each phase of the study and those loss to follow-up is shown in Figure 3.1

3.3 Ethical consideration

The TASOAC study was approved by the Tasmanian Health and Medical Research Ethics Committee Ethics (Approval Number: H6488). Written informed consent was obtained from all participants.

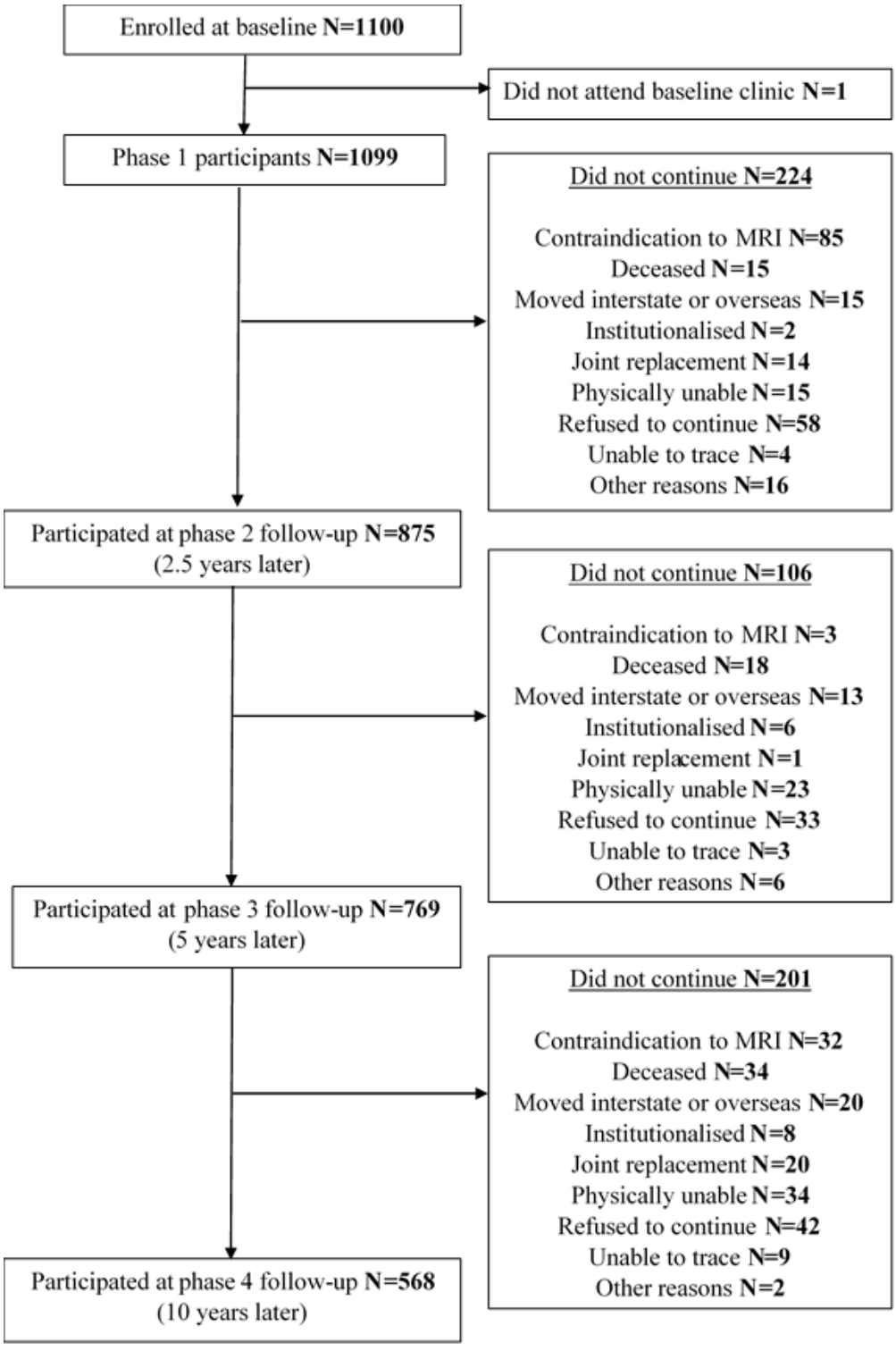

Figure 3.1 Flowchart describing number of participants and those loss to follow-up at each phase of TASOAC study.

3.4 Outcome measures

3.4.1 Body composition

Whole and regional body composition of the participants were measured using dual-energy X-ray absorptiometry (DXA; Hologic Delphi, Hologic, Waltham USA). Appendicular lean mass (ALM), in kilograms, was calculated as the sum of lean mass in the upper and lower limbs. Weight was measured to the nearest 0.1 kilogram using electronic scales (Heine, Dover, USA) with shoes and heavy clothing removed. Height was measured to the nearest 0.1 centimetre using Leicester stadiometer (Invicta, Leicester, UK), with shoes, socks and headgear removed. Body mass index was calculated as weight (kg) divided by height (m) squared.

3.4.2 Muscle strength and muscle quality

Lower-limb muscle strength was measured to the nearest kilogram simultaneously for both limbs using a dynamometer (TTM Muscular Meter, Tokyo, Japan). Two trials were recorded and the average of the two trials was taken as previously described [185]. Hand grip strength in pounds per square inch (psi) was measured using a pneumatic handheld bulb dynamometer (North CoastTM bulb dynamometer; adult 0-30 psi, model no. 70154). The mean of the right and left hand grip strength was calculated for each participant. The intra-class correlation coefficients of the first and second trial for lower-limb muscle strength and hand grip strength measurements were 0.95 (95% CI: 0.94 – 0.96) and 0.96 (95% CI: 0.92 – 0.97) respectively.

Upper-limb muscle quality was defined as hand grip strength divided by the sum of lean mass in the right and left upper limb and Lower-limb muscle quality was defined as lower limb muscle strength divided by the sum of lean mass in the left and right lower limb [63].

3.4.3 Falls risk

Falls risk at was assessed at baseline, 2.5, 5 and 10 years follow-up using the short form Physiological Profile Assessment (PPA) (Prince of Wales Medical Research Institute, Sydney, Australia), a valid and reliable tool used to identify individuals who are at risk of falls [186]. The PPA assesses five physiological domains (visual contrast sensitivity, reaction time, knee extension strength, proprioception and postural sway on foam) and a standardized falls risk score is calculated for each individual using these five domains. Individuals with a falls risk score of less than zero are regarded as having a low risk of falls, between zero and one are at a mild risk of falls, between one and two are at a moderate risk of falls and those with a falls risk score of more than 2 are at a high risk of falls. The PPA has been shown to have 75% accuracy in predicting multiple falls among older people [187].

3.4.4 Fracture

At each study visit participants were asked to list, by location, any fractures they had since their previous clinic visit. Those who experienced at least one fracture between the baseline and 10-year follow-up assessment were coded as ‘1’ (incident fracture) and those without any fracture were coded ‘0’ (no incident fracture).

3.4.5 Mortality

Data on mortality was collected until August 2015. Mortality over 10 years was ascertained through national and state death registries.

3.4.6 Health-related quality of life (HRQoL)

HRQoL was assessed at baseline, 2.5, 5 and 10 years using the Assessment of Quality of life (AQoL-4D) questionnaire. The AQoL-4D is a validated generic questionnaire designed for the Australian population [188]. The questionnaire consists of 12 items covering four dimensions and each dimension has three items. The four dimensions and their corresponding items are: (1) independent living (self-care, activities of daily living), (2) physical senses (sight, hearing and communication), (3) social relationships (social isolation, relationship and family role) and (4) psychological wellbeing (sleep, anxiety and pain). The scores for items in each domain were transformed and summed to a life-death utility scale that ranges from 1.00 (full HRQoL) to 0.00 (death-equivalent health state) to –0.04 (health states worse than death) [189, 190]. The minimum important difference in AQoL score for the Australian population is 0.06 [190]. This score provides a measure of the smallest difference in AQoL score that is considered to be of a significant change in the health state of Australians [190].

3.4.7 Physical activity

Ambulatory physical activity was assessed at baseline, 2.5 and 5 years. Baseline assessment was measured over seven consecutive days using a pedometer (Omron HJ-003 & HJ-102; Omron Healthcare, Kyoto, Japan) worn on the waist band or belt

above their dominant leg. Participants were given a diary in which to record the duration of pedometer use and daily step counts. At 2.5 years follow-up Yamax pedometers (Yamax SW-200; Yamax USA, San Antonio, TX, USA) were given to the majority (98%) of the participants. A strong linear correlation (r=0.88) was found between the estimates of the two types of pedometer, but the Omron brand recorded higher mean steps. Yamax pedometers were used by all participants at 5 years. Baseline and 2.5 years Omron estimates were multiplied by a correction factor of 0.91 to provide comparability between mean estimates for Omron and Yamax pedometers [191].

The intensity of physical activity was assessed in a subset of 637 participants using an accelerometer (ActiGraph GT1M). Participants were instructed to wear the accelerometer for 7 consecutive days, and were provided with a daily diary to record when the accelerometer was worn and when it was removed (for instance, during swimming or showering). Data were included in the analysis if the participants wore the accelerometer for 5 valid days or more; with a valid day being one in which the accelerometer was worn for at least 10 hours. Details about accelerometer data cleaning and the cut-points used for intensity (sedentary, light, moderate, and vigorous) have been described in detail previously [68]. Vigorous physical activity was combined with moderate physical activity because few older adults engaged in vigorous physical activity. Moderate-to-vigorous physical activity (MVPA) was log-transformed as the variable was skewed to the right.

3.4.8 Knee pain, stiffness and functional limitation

Knee pain, stiffness and functional limitation were assessed by self-administered questionnaire using the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) at each study visit. WOMAC is a validated and widely used measure of symptoms and disability in patients with osteoarthritis [192]. The three WOMAC sub-scales: knee pain, stiffness and functional limitation were assessed separately with 5, 2 and 17 questions respectively. Response to each question ranges from 0 (no symptom) to 9 (most severe knee pain, stiffness or functional limitation). Response in each sub-scale was summed to create a score for knee pain (range: 0–45), stiffness (range: 0–18) and functional limitation (range: 0–153). All three sub-scales were also summed to create a WOMAC global score (range: 0–216).

3.4.9 Serum 25-hydroxyvitamin D [25(OH)D]

Serum 25(OH)D was assessed at baseline, 2.5 and 10-year follow-up. Serum samples from blood drawn from the participants were treated initially with acetonitrile to rapidly extract vitamin-D and other hydroxylated metabolites. Thereafter 25(OH)D was assayed using a liquid-phase radioimmunoassay (Immunodiagnostics Systems Ltd), which detects both 25(OH)D2 and 25(OH)D3. The intra-assay and inter-assay coefficients of variation were 1.8% and 3.3% respectively. Participants had their baseline and follow-up interview at different seasons and as 25(OH)D is known to vary with seasons, we de-seasonalised the 25(OH)D measurement as previously described [15] to account for differences in the time of the year that blood was taken.

3.5 Covariates

At each phase of the TASOAC study a questionnaire was mailed to study participants to collect information about age, sex, employment status, smoking status, medical history, including a previous diagnosis of diabetes, rheumatoid arthritis and cardiovascular disease (hypertension, bronchitis/emphysema, or heart attack).

3.6 Study factors

Table 3.1 shows the study factors for each research question addressed in the thesis. Each study is also described in their respective Chapter.

3.7 Statistical analyses

Description of statistical analyses performed for each study are presented in their respective chapters. However, a detailed description of the novel longitudinal analysis method used in Chapter 4 and 6 is presented below, while a shortened version is described in each Chapter. All statistical analyses were performed using Stata for Windows version 12 and 13 (StataCorp LP, Texas, US).

Table 3.1 Description of outcome variables, predictor variables, and covariates examined in the thesis, by Chapter.

Chapter	Outcome variable/s	Predictor variables	Covariates
4	LLM, LMS, LMQ	Physical activity 25(OH)D Knee pain and dysfunction	Age, sex, chronic conditions, employment status and smoking status
5	Falls risk Fracture Mortality	LMQ, UMQ, LMS, HGS, ALM/HH, ALM/BMI, ALM/W, ALMR	Age
6	Falls risk	Physical activity 25(OH)D Knee pain and dysfunction	Age, sex, chronic conditions, employment status, smoking status and appendicular lean mass and fat mass
7	HRQoL	ALM/BMI, LMS and HGS	Age, sex, self-reported pain, chronic conditions and physical activity
8	Fracture Mortality	ALM/BMI, HGS, BMD	Age, sex, 25(OH)D, chronic conditions and physical activity

LLM: Lower-limb lean mass; LMS: Lower-limb muscle strength; HGS: Handgrip strength; LMQ: Lower-limb muscle quality; UMQ: Upper-limb muscle quality; 25(OH)D: Serum 25-hydroxy vitamin D; ALM/HH: Appendicular lean mass/height2; ALM/BMI: Appendicular lean mass/body mass index; ALM/W: Appendicular lean mass/weight; ALMR: Residual of appendicular lean mass on height and total body fat; HRQoL: Health-related quality of life; BMD: Bone mineral density

3.7.1 Description of time-varying predictor variables

This thesis employs an advanced statistical method to examine how variability in physical activity, 25(OH)D, knee pain and dysfunction within the same individual over time is related to muscle changes and falls risk. Traditionally, research in this area has focused on examining how these risk factors differ between individuals (between-person comparison) but less well recognised is how variability within the same individual (within-person comparison) over time relates to muscle changes and falls risk. This is important to investigate because the information we get from between-person analysis (e.g., the magnitude and direction of effects) might be quite different from what a within-person analysis tells us.

Physical activity, 25(OH)D, knee pain and dysfunction were assessed at multiple time-point in the TASOAC study, and the values of these variables differed for most participants on each measurement occasion. Hence, these variables are said to be ‘time-varying' or ‘time-dependent covariates' [193, 194]. Time–varying predictors provide two sources of information in longitudinal analysis. These are within–person and between–person effects. The between–person component of the time-varying predictor is an individual’s average 25(OH)D; physical activity and WOMAC score across all measurement occasions. The within–person component is the deviation of an individual’s measurement on a particular phase of the study from his or her average score across all measurement occasions. Within–person (level 1) and between–person (level 2) effects are a ‘linked pair’ and are jointly referred to as a multilevel model [194]. Incorrect specification of a time–varying predictor in the analysis of longitudinal data will result in biased model effects [193]. For example,

analysing time-varying predictors without separating the variable into level 1 (within-person) and level 2 (between-person) effects is based on the assumption that within- and between-cluster effects are equal [195]. This is a strong assumption and it is not always true for time-varying covariates [196, 197]. To ensure there is sufficient variance to warrant decomposing the predictor variables into between-person and within-person effects we calculated intra-class correlation coefficients (ICCs) for each predictor variable using an intercept only model [193, 198].

Linear mixed-effect regression models were then used to estimate the between-person and within-person effects of 25(OH)D, physical activity, and knee pain and dysfunction on falls risk and muscle changes. We decomposed each time-varying covariate into between- and within-persons components. The statistical model (without adjustment for confounders), using 25(OH)D as an example of a predictor variable and muscle strength as outcome variable, is shown below.

$$Muscle\ strength_{ij} = \beta_0 + \beta_1\left(25OHD_{ij} - Mean\ 25OHD_i\right) + \beta_2(Mean\ 25OHD_i) + \cup_{0j} + e_{ij}$$

Where, *muscle strength*$_{ij}$ is the muscle strength for person *i* at time *j*, β_0 is the intercept, *mean 25OHD*$_i$ is individual's average vitamin-D across all measurement occasions, *25OHD*$_{ij}$ is individual's absolute vitamin-D value at each measurement occasion, U_{0j} is the between–persons random components or error, and e_{ij} is the within–person random error. β_1 and β_2 are the level 1 (within–persons) and level 2 effects (between–persons) respectively.

A positive beta coefficient for a level 2 predictor (between-person) suggests that an individual with a higher 10-year average 25(OH)D, higher 10-year average physical activity or lower 10-year average WOMAC score, would be estimated to have a higher 10-year mean muscle strength. A positive beta coefficient for the level 1 predictor (within-person) would imply that, at a time-point when an individual has a higher 25(OH)D, higher physical activity or lower WOMAC score than his or her 10-year average score, the individual would be estimated to have a higher muscle strength at that time-point. Model fit were accessed using likelihood ratio test, Akaike Information criterion and Bayesian Information Criterion [199].

Chapter 4: Longitudinal Associations of Serum 25-hydroxyvitamin-D, Physical Activity, and Knee Pain and Dysfunction with Muscle Loss in Community-dwelling Older Adults

4.1 Abstract

Aim: To describe the associations of between-person and within-person variability in serum 25-hydroxyvitamin D (25(OH)D), physical activity (PA) and knee pain and dysfunction with muscle mass, strength and muscle quality over 10 years in community-dwelling older adults.

Method: Participants (n=1033; 51% women; mean age 63±7.4 years) were measured at baseline, 2.5, 5, and 10 years. Lower-limb lean mass (LLM) was assessed using DXA, lower-limb muscle strength (LMS) using a dynamometer; and lower-limb muscle quality (LMQ) calculated as LMS/LLM. Knee pain and dysfunction were assessed using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index. PA was measured using pedometers. Linear mixed effect regression models, with adjustment for confounders, were used to estimate the association of within-person and between-person variability in PA, 25(OH)D and WOMAC score with muscle mass, strength and muscle quality.

Results: Both between-person and within-person increases in PA were associated with LLM, LMS and LMQ (all $P<0.05$). Within-person and between-person increases in knee pain and dysfunction were associated with LLS and LMQ but not LLM (all $P<0.05$).

Between-person effects showed that higher average 25(OH)D was associated with higher 10-year average LLM, LMS and LMQ (all $P<0.05$); whereas, within person increases in average 25(OH)D was associated with a higher LMS, LMQ but not LLM.

Conclusions: Variability in 25(OH)D, pain and dysfunction within an individual over time relate to muscle changes in that individual. Increasing one's own physical

activity level further increases muscle mass, strength and quality supporting the clinical recommendation of promoting PA to reduce age-related muscle loss.

4.2 Introduction:

Age-related loss of skeletal muscle mass, strength and muscle quality is a major public health concern that is associated with functional disability, poor quality of life and mortality in older people [71, 200-202]. While loss of muscle mass and function increases with age, significant variability exists between individuals in the rate of loss of muscle mass and function [203]. Traditionally, analysis has focused on examining how risk factors for loss of muscle mass and function differ between individuals (between-person comparison). These studies showed that age-related loss of muscle mass and strength is more prevalent in older adults with lower levels of serum 25-hydroxyvitamin D (25(OH)D) [104, 105, 204], physical activity [68, 71, 185] and higher levels of knee pain and functional limitation [71, 72]. As a result, public health efforts have been informed by findings from between-person comparisons but less well recognised is how variability within the same individual (within-person comparison) over time is related to muscle changes. This is important to investigate because the information we get from between-person analysis (for example the magnitude and direction of effects) might be quite different to what a within-person analysis tells us. Besides, neither can be inferred from the other [205]. Statistical methods, such as multilevel models that properly capture the within-person processes can be used to tell us whether changes within an individual over time relate to changes in muscle in that same individual [193]. Findings from within-person comparison are vital for formulating policies aimed at improving population health by

promoting good health behaviours like physical activity at the individual level. This could include person-centered public health messages that highlight the benefits of improving one's own level of physical activity.

To our knowledge, there are no published studies describing associations of within-person variability in physical activity, 25(OH)D, knee pain and dysfunction with loss of muscle mass, strength and muscle quality in community-dwelling older people. Therefore, the aim of this study was to describe the associations of between-person and within-person variability in 25(OH)D, physical activity, knee pain and dysfunction with age-related loss of skeletal muscle mass, strength and muscle quality over 10 years in community-dwelling older adults. We hypothesized that older adults with a lower mean level of physical activity, 25(OH)D and higher average level of knee pain and dysfunction would have a lower muscle mass, strength and muscle quality. Furthermore, at time-points when an individual had a lower level of 25(OH)D, physical activity and higher knee pain and dysfunction than their own individual average, they would also have lower muscle mass, strength and muscle quality.

4.3 Data and Methods

The Tasmanian Older Adult Cohort (TASOAC) study is a prospective, population-based study primarily aimed at examining the causes and progression of osteoarthritis. Participants aged 50 years and older were selected using sex-stratified random sampling from the electoral roll in Southern Tasmania (population 229,000). A total of 1099 adults (response rate = 57%) consented to participate. Participants were excluded if they had any implants that would prevent them from undergoing an MRI

or they were living in a nursing home. Participants attended a clinic at the Menzies Institute for Medical Research, Hobart, Tasmania between March 2002 and September 2004, and follow–up clinic assessments 2.5, 5, and 10 years later. The study was approved by the Southern Tasmanian Health and Medical Research Ethics Committee and written informed consent was obtained from all participants.

4.4 Outcome measures

4.4.1 Body composition and anthropometrics

Body composition was measured using dual energy X-ray absorptiometry (DXA; Hologic Delphi, Hologic, Waltham USA). Leg lean muscle mass (kg), was calculated as the sum of lean mass in both lower-limbs. Weight (kg) was measured using electronic scales (Heine, Dover, USA). Height (cm) was measured using the Leicester stadiometer (Invicta, Leicester, UK).

4.4.2 Lower-limb muscle strength and muscle quality

Lower-limb muscle strength (LMS) in kilograms was measured simultaneously for both limbs using a dynamometer (TTM Muscular Meter, Tokyo, Japan). Participants stood on the back of a dynamometer platform with their backs against a wall and knee flexed to 115°. A bar was attached to the dynamometer, and participants lifted the bar using their lower-limbs only to maximum contractile force, whilst maintaining proper head and neck posture. This test assessed the isometric strength of the whole lower-limbs, but predominantly of the quadriceps and hip extensors. Two trials were recorded, with the mean score taken as the criterion value for lower-limbs muscle

strength [185]. The intra-class correlation coefficient (ICC) for the first and second trial was 0.95 (95% CI: 0.94–0.96). Leg muscle quality (LMQ), was calculated as LMS divided by the sum of DXA-derived lean mass of the two lower-limbs [206].

4.5 Predictor variables

4.5.1 Physical activity

Habitual physical activity was assessed at baseline, 2.5 and 5 years. Baseline assessment was assessed over seven consecutive days using a pedometer (Omron HJ-003 & HJ-102; Omron Healthcare, Kyoto, Japan) worn on the waist band or belt above their dominant lower-limb. Participants were given a diary in which to record the duration of pedometer use and daily step counts. At 2.5 years follow-up Yamax pedometers (Yamax SW-200; Yamax USA, San Antonio, TX, USA) were given to the majority (98%) of the participants. A strong linear correlation (r=0.88) was found between the estimates of the two types of pedometer, but the Omron brand recorded higher mean steps. Yamax pedometers were used by all participants at 5 years. Baseline and 2.5 year Omron estimates were multiplied by a correction factor of 0.91 to provide comparability between mean estimates for Omron and Yamax pedometers [191]. Beta coefficients in the regression models were scaled to 1000 steps per day for ease of interpretation.

4.5.2 Knee pain, stiffness and functional limitation

Knee pain, stiffness and functional limitation were assessed by self-administered questionnaire using the Western Ontario and McMaster Universities osteoarthritis

index (WOMAC) at each study visit. WOMAC is a validated and widely used measure of symptoms and disability in patients with osteoarthritis [192]. The three WOMAC sub-scales: knee pain, stiffness and functional limitation were assessed separately with 5, 2 and 17 questions respectively. Response to each question ranges from 0 (no symptom) to 9 (most severe knee pain, stiffness or functional limitation). Response in each sub-scale was summed to create a score for knee pain (range: 0–45), stiffness (range: 0–18) and functional limitation (range: 0–153). All three sub-scales were also summed to create a WOMAC global score (range: 0–216).

4.5.3 Serum 25-hydroxyvitamin D

25(OH)D was assessed at baseline, 2.5 and 10-year follow-up. Serum samples from blood drawn from the participants were treated initially with acetonitrile to rapidly extract vitamin-D and other hydroxylated metabolites. Thereafter 25(OH)D was assayed using a liquid-phase radioimmunoassay (Immunodiagnostics Systems Ltd), which detects both 25(OH)D2 and 25(OH)D3. The intra-assay and inter-assay coefficients of variation were 1.8% and 3.3% respectively. Participants had their baseline and follow-up interview at different seasons and as 25(OH)D is known to vary with seasons, we de-seasonalised the 25(OH)D measurement as previously described [15] to account for differences in the time of the year that blood was taken.

4.6 Potential confounders

Age, sex, medical history, including a previous diagnosis of diabetes, rheumatoid arthritis, cardiovascular disease (hypertension, bronchitis/emphysema, or heart

attack), as well as employment status, and smoking history were recorded using a questionnaire.

4.7 Data analysis

Measurements for physical activity, 25(OH)D, and WOMAC scores varied across occasions for individuals, and were modelled as time-varying predictors [193, 194]. Time–varying predictors provide two sources of information in longitudinal analysis; consequently, we decomposed each time-varying predictor into between- person and within-person components. The between–person component of the time-varying predictor is an individual's average 25(OH)D, physical activity and WOMAC score across all measurement occasions. The within–person component is the deviation of an individual's measurement at a particular phase of the study from his or her average score across all measurement occasions. We first calculated intra-class correlation coefficients (ICCs) for each predictor variable to ensure there was sufficient variance to warrant decomposing the predictors into between-person and within-person effects [193, 198]. All ICC of our predictor variables were >0.3, suggesting substantial variability in each predictor variable[198].

Linear mixed effect regression models were used to estimate the association of between-person and within-person variability in 25(OH)D, physical activity, and WOMAC scores over 10 years with LLM, LMS and LMQ. Models were adjusted for age, sex, number of chronic conditions, employment status and smoking status. Multiplicative interaction between age, sex and between-person and within-person variability in serum 25(OH)D, physical activity, knee pain and dysfunction was assessed for each outcome variable. All models were estimated using the maximum

likelihood method. The fit of models with different fixed and random effects were compared using the likelihood ratio test and Akaike Information Criterion [199]. Data was analysed using Stata version 13 (StataCorp, TX, USA).

4.8 Results

A total of 1033 participants with complete body composition and muscle assessments at baseline were included in the analysis. Of these, 853 (82%), 752 (73%) and 559 (54%) respectively attended the 2.5, 5 and 10 years follow-up assessments. Participants were lost to follow-up because of reasons such as death, withdrawal of consent, institutionalization, moving interstate or overseas and having a joint replacement. Compared to those who completed the 10 year follow-up assessment, participants lost to follow-up were older at baseline (64.7±8.0 vs. 61.4±6.5 years, P<0.001), had lower lean muscle mass (23.9±5.3 vs. 24.8±5.3 kg, P=0.005), weaker lower-limb muscle strength (87.7±47.0 vs. 96.9±50.5 kg, P=0.003) and muscle quality (5.3±2.3 vs. 5.7±2.4, P=0.019) but no difference in the proportions of males and females was observed (P=0.524).

Baseline characteristics of the participants are shown in Table 4.1. The mean age of the participants at baseline was 63±7.4 and 51% were female. The associations of between-person and within-person variability in 25(OH)D, physical activity, knee pain and dysfunction with LLM, LMS and LMQ are shown in Table 4.2.

4.8.1 Physical activity and LLM, LMS and LMQ

Both between-person and within-person increases in physical activity were associated with muscle changes (between-person: LLM (β=0.03; 95% CI 0.02, 0.05), LMS (β=1.25; 95% CI 0.61, 1.88) and LMQ (β=0.10; 95% CI 0.06, 0.13)); within person: LLM (β=0.02; 95% CI 0.001, 0.04), LMS (β=0.56 95% CI 0.01, 1.10) and LMQ (β=0.04; 95% CI 0.01, 0.07)). There was an interaction between sex and between-person variability in physical activity and LMQ, such that the positive association was stronger in women (β=0.14, 95% CI: 0.09, 0.19) compared to men (β=0.06, 95% CI: 0.01, 0.11).

4.8.2 Knee pain and dysfunction and LLM, LMS and LMQ

Between-person increase in WOMAC global score was associated with a significantly lower LMS (β= –0.21; 95% CI –0.28, –0.13), LMQ (β= –0.02; 95% CI –0.02, –0.01) but not LLM (β=0.001; 95% CI:–0.002, 0.003). Similar associations were observed for the WOMAC subscales. Sex modifies the relationship between LMQ and between-person variability in WOMAC knee pain sub-scale (Men: β= –0.06, 95% CI: –0.09, –0.03; women: β= –0.10, 95% CI: –0.12, –0.07) and WOMAC knee dysfunction subscale (Men: β= –0.02, 95% CI: –0.03, –0.01; women: β= –0.03, 95% CI: –0.04, –0.02), such that the negative associations were stronger for women compared to men.

Within-person increase in WOMAC global score was associated with a lower LMS (β= –0.09; 95% CI –0.15, –0.03), LMQ (β= –0.006 95% CI –0.01, –0.002) but not LLM (β= 0.002 95% CI –0.0003, 0.004). Furthermore, at time-points when WOMAC

knee dysfunction sub-scale scores were higher than average, LMS (β= –0.14 95% CI –0.22, –0.06), LMQ (β= –0.01 95% CI –0.01, –0.003) but not LLM (β= 0.002 95% CI –0.001, 0.005) were significantly lower. No significant within-person association was found between WOMAC knee pain and knee stiffness subscales and LLM, LMS and LMQ. The association between within-person variability in WOMAC global score and LMQ was modified by age such that the association was significant in participants aged 50-69 years (β= –0.01, 95% CI:–0.01, –0.004) but not significant in participants aged 70 years and older β=0.005, 95% CI:–0.001, 0.01). A similar relationship was observed between within-person variability in knee dysfunction subscale and LMS (50-69 years: β= –0.19, 95% CI:–0.28, –0.10 versus 70 years and older: β=0.04, 95% CI:–0.10, 0.17).

4.8.3 Serum 25(OH)D and LLM, LMS and LMQ

Between-person analysis showed that participants with a higher 10-year average 25(OH)D had a significantly higher LLM (β=0.005; 95% CI: 0.001, 0.01), LMS (β=0.16; 95% CI: 0.05, 0.27) and LMQ (β=0.01; 95% CI: 0.01, 0.02). There was a significant interaction between sex and between-person increase in 25(OH)D and LLM (P-value for interaction=0.09), such that the association was stronger for men (β=0.008, 95% CI:0.003, 0.01) than women (β=0.0003, 95% CI: –0.003, 0.004).

Within-person increase in 25(OH)D was associated with higher LMS (β=0.10; 95% CI: 0.03, 0.17), LMQ (β=0.01; 95% CI: 0.002, 0.01) but not LLM (β=0.002; 95% CI: –0.001, 0.004).

Table 4.1: Baseline characteristics of participants in the Tasmanian Older Adult Cohort (TASOAC) study (N= 1033)

Variables	Mean	SD*
Age (years)	63.0	7.4
Female, n (%)	525	51
Height (cm)	167.1	9.0
Weight (kg)	77.8	14.8
Body mass index (kg/m^2)	27.8	4.7
Serum 25-hydroxyvitamin D (nmol/L)	52.6	18.7
Appendicular lean mass, Kg	24.5	14.7
Physical activity (steps/day)	8659	3370
Total body fat mass, Kg	28.1	8.6
Current smoker, n (%)	523	51
Number of chronic conditions	1.5	1.4
Currently employed, n (%)	416	40
WOMAC	15.8	27.3
WOMAC sub-scales		
WOMAC knee pain	3.5	6.0
Knee stiffness	1.6	2.6
Functional limitation	10.8	19.9

*Data are presented as mean (standard deviation (SD)) unless otherwise specified.

Table 4.2: Association of between-person† and within-person variability‡ in serum 25-hydroxyvitamin D, physical activity (PA), knee pain and dysfunction with lower-limb lean mass, lower-limb muscle strength and muscle quality (N=1033)

	Lower-limb lean mass, Kg		Lower-limb muscle strength, Kg		Lower-limb muscle quality, Kg/Kg	
Predictor variables	Between-person effect β (95% CI)	Within-person effect β (95% CI)	Between-person effect β (95% CI)	Within-person effect β (95% CI)	Between-person effect β (95% CI)	Within-person effect β (95% CI)
PA (per 1000 steps/day)	**0.03 (0.02, 0.05)**	**0.02(0.001, 0.04)**	**1.25 (0.61, 1.88)**	**0.56 (0.01, 1.10)**	**0.10 (0.06, 0.13)**	**0.04 (0.01, 0.07)**
WOMAC global score	0.001 (–0.002, 0.003)	0.002(–0.0003, 0.004)	**–0.21 (–0.28, –0.13)**	**–0.09 (–0.15, –0.03)**	**–0.02 (–0.02, –0.01)**	**–0.006 (–0.01, –0.002)**
WOMAC sub-scales						
Knee pain	0.004 (–0.01, 0.01)	0.01(–0.0003, 0.02)	**–0.85 (–1.20, –0.51)**	–0.18 (–0.42, 0.07)	**–0.08 (–0.10, –0.06)**	–0.01 (–0.03, 0.003)
Knee stiffness	0.01 (–0.01, 0.04)	0.01(–0.01, 0.03)	**–1.85 (–2.63, –1.07)**	–0.29 (–0.81, 0.23)	**–0.19 (–0.23, –0.14)**	–0.02 (–0.06, 0.01)
Knee dysfunction	0.001 (–0.002, 0.004)	0.002(–0.001, 0.005)	**–0.29 (–0.39, –0.19)**	**–0.14 (–0.22, –0.06)**	**–0.03 (–0.03, –0.02)**	**–0.01 (–0.01, –0.003)**
Serum 25(OH)D(nmol/L)	**0.005 (0.001, 0.01)**	0.002(–0.001, 0.004)	**0.16 (0.05, 0.27)**	**0.10 (0.03, 0.17)**	**0.01 (0.01, 0.02)**	**0.01 (0.002, 0.01)**

Data in bold indicate statistical significance at $P < 0.05$

Models are adjusted for age, sex, number of chronic conditions (diabetes, rheumatoid arthritis, cardiovascular disease (hypertension, bronchitis/emphysema, or heart attack)), employment status (currently employed *vs.* not currently employed), smoking status, linear time and quadratic time.

†Beta-coefficients expressed as change in 10-year average of the outcome variable per 1 unit increase in the 10-year average predictor variable (25(OH)D, WOMAC and PA)

‡Beta-coefficients expressed as change in outcome variable per 1 unit deviation from the participant's 10-year mean predictor score (25(OH)D, WOMAC and PA)

4.9 Discussion

To our knowledge, this is the first prospective study to determine the associations between both within-person and between-person variability in serum 25(OH)D, physical activity and knee pain and dysfunction and LLM, LMS and LMQ in community-dwelling older adults. Consistent with between-person findings, fluctuations in 25(OH)D, knee pain and dysfunction and physical activity within an individual were related to variations in muscle in that individual. Importantly, this work builds on our knowledge from between-person analysis, as it demonstrates that within-person variability in these factors have independent effects on muscle. Specifically, having higher 25(OH)D and lower knee pain and dysfunction compared to an individual's average was associated with greater muscle strength and quality but not muscle mass. Furthermore, when participants engaged in more physical activity than their average level, they had higher LMM, LMS and LMQ.

Both between-person and within-person increases in physical activity were associated with a higher muscle mass, strength and muscle quality. The within person findings suggest that, irrespective of an individual's usual level of physical activity, further increases in physical activity have additional beneficial effects on muscle mass, strength and muscle quality. For instance, at time-points when an individual (either with higher or lower 10-year average physical activity) increased their steps-per-day by 1000, that individual had a 0.56 kg increase in LMS. The effect of physical activity on muscle was stronger in the between-person analysis (e.g. a 1000 steps/day increase resulted in a 1.25 kg increase in 10-year average LMS). The discrepancy between the within- and between-person estimates may be because error variance associated with

important individual differences are reduced in the within-person estimates compared to the between-person comparisons. For instance, differences such as genetic makeup, pain perception and motivation to engage in physical activity, which are not captured in the between-person comparison, are held constant in the within-person comparison. Nonetheless, our previous study[185] and others[68, 71] report that pedometer determined physical activity is associated with sarcopenia. Hence, physical activity has been recognised as one of the most feasible and inexpensive strategies to delay age-related loss of mass and function with clinical guidelines emphasizing physical activity to promote health including preventing incidence of sarcopenia in older people [97, 207]. We found that the magnitude of the associations of between-person increases in physical activity with LMQ was higher in women compared to men. This observation has been seen in some [185, 208], but not all previous studies [209]. Although the underlying mechanism of this sex difference is unclear, one potential explanation may be that because women have smaller muscles, therefore ambulatory activity stimulates a greater improvement in muscle quality in women than men who may require a greater stimulus. This present study builds on previous knowledge by showing that increasing one's own physical activity above their 'usual' level results in further increases in lower-limb lean mass, muscle strength and quality.

Within-person increase in WOMAC global score and functional limitation sub-scale was associated with a lower muscle strength and quality, whereas, between-person increase in WOMAC global score and knee pain, stiffness and functional limitation sub-scales were associated with lower muscle strength and quality. Muscle mass was not associated with WOMAC global score or the sub-scales in either between or within person analysis. Knee pain and dysfunction may lead to lower muscle strength

and muscle quality through activity limitation due to pain-related fear [210, 211] or via reflex muscle inhibition [70, 212]. The significant within-person association suggests that at time-points when the participants reported higher knee dysfunction, they may also have experienced greater activity limitation, thus, they had a weaker lower-limb muscle strength and muscle quality. It could also imply that the participants were less able to exert a maximal contraction due to actual or anticipated pain, which may explain why the decrease in muscle strength does not translate to a loss of muscle mass. Pain represents a major clinical symptom in older people and it is a predictor of transition towards sarcopenia [71, 213]. Yet, it is under-assessed and undertreated potentially due to the perception that pain is an unavoidable consequence of ageing [214]. The within-person analysis emphasizes the importance of adequate pain management in older people, particularly on occasions when their pain is higher than their 'usual' pain level, in order to prevent further loss of muscle strength and quality. Interestingly, the between-person association between knee pain and dysfunction and muscle parameters was stronger in women compared to men. This finding is consistent with our previous study [72] and may be due to the fact women are less capable of generating force in the presence of pain during strength testing compared to men [215]. Furthermore, the within-person association between pain and muscle measures was modified by age such that an increase in knee pain was associated with a higher loss of muscle strength and quality in the younger (50-69 years) compared to the older age category (70 years and above). The reason for this is unclear. Notably, the association of between-person and within-person variability in knee pain and dysfunction with muscle strength and quality are mostly independent of physical activity (Table 4.3). This demonstrates that there are multiple pathways

including direct inhibition of muscle function through which knee pain and dysfunction contributes to loss of muscle function [70, 212].

The between-person findings between 25(OH)D and muscle mass, strength and quality suggest that long-term maintenance of 25(OH)D is beneficial for muscle. These findings are supported by our previous work [105]. Notably, the magnitude of the association of between-person difference in 25(OH)D and LLM was higher in men compared to women, potentially due to higher physical activity in men. Furthermore, there was evidence for a dynamic within-person relationship between 25(OH)D and muscle strength and quality but not muscle mass. This suggests that, irrespective of their 'usual' level of 25(OH)D, variability in 25(OH)D around an individual's mean value results in further improvements in muscle strength and quality but not muscle mass. Indeed, improvement in muscle strength do not necessarily overlap with an increase in mass as the two processes may be the results of different pathophysiological mechanisms [216].The within-person increase in muscle strength and quality but not muscle mass may be related to the role of vitamin D in muscle fibre neuromuscular junction [217]. These findings highlight that vitamin D plays a role in age-related skeletal muscle changes and that further increases in 25(OH)D above an individual's average has additional benefit to muscle strength and muscle quality.

This study has a number of strengths including the use of a person-mean centering analysis approach, allowing us to disentangle the within-person and between-person effects of the predictor variables. This is particularly useful as we were able to show both between-person and within-person variability in 25(OH)D, physical activity and

knee pain and dysfunction were independently contributing to muscle mass, strength and muscle quality. Another strength of this study is the use of objective measures of physical activity which likely increases the accuracy of our estimates. However, this study also has a number of limitations. Firstly, 47% of participants recruited at baseline were lost to follow-up over 10 years. Such missing data is not unexpected in a long-term prospective study involving older people. The missing data were accommodated by using maximum likelihood estimation which uses available data for model estimation, rather than casewise deletion. Secondly, although we hypothesised that higher knee pain and dysfunction would result in lower muscle mass, strength and muscle quality, reverse causality is also possible where muscle weakness could lead to an increase in knee pain. Our study focused on the association of between-person and within-person variability in serum 25(OH)D, physical activity with LLM. However, it is possible that serum 25(OH)D and physical activity have a systemic effect on muscle mass and function. Unlike LLM, we found no evidence for an association of between-person (β= –0.04, 95% CI: 0.10, 0.02) and within-person (β=0.01, 95% CI: –0.02, 0.04) increase in physical activity and ALM, potentially due to the large role the lower-limbs play in mobility. Furthermore, we found no association between within-person (β=0.0002; 95% CI: –0.004, 0.004) and between-person increase in 25(OH)D (β=–0.004, 95% CI: –0.01, 0.01) and ALM. The reason for this observation is unclear but it is consistent with studies showing evidence for an association between vitamin D and specific muscle groups [218].

In conclusion, our findings demonstrate that both between-person and within-person fluctuations in 25(OH)D, pain and dysfunction and physical activity were associated with muscle changes. The finding that within-person variation in physical activity

levels were associated with within-person variation in muscle mass, strength and quality is reassuring and it adds a new perspective to public health efforts aimed at promoting physical activity in older people. It shows that increasing one's own ambulatory physical activity further increases muscle mass, strength and quality.

Table 4.3 (supplementary Table): Association of between-person† and within-person‡ variability in serum 25-hydroxyvitamin D, knee pain and dysfunction with lower-limb lean mass, lower-limb muscle strength and muscle quality (N=1033)

Predictor variables	Lower-limb lean mass, Kg		Lower-limb muscle strength, Kg		Lower-limb muscle quality, Kg/Kg	
	Between-person effect β (95% CI)	Within-person effect β (95% CI)	Between-person effect β (95% CI)	Within-person effect β (95% CI)	Between-person effect β (95% CI)	Within-person effect β (95% CI)
WOMAC global score	0.001 (–0.002, 0.003)	0.001(–0.001, 0.004)	**–0.20 (–0.28, –0.12)**	**–0.08 (–0.15, –0.01)**	**–0.02 (–0.02, –0.01)**	–0.004 (–0.01, 0.00002)
PA (per 1000 steps/day)	**0.04 (0.02, 0.06)**	**0.02(0.002, 0.04)**	**0.99 (0.35, 1.63)**	0.50 (–0.04, 1.05)	**0.07 (0.04, 0.11)**	**0.04 (0.002, 0.07)**
WOMAC sub-scales						
Knee pain	0.004 (–0.01, 0.01)	0.01(–0.01, 0.02)	**–0.83 (–1.19, –0.47)**	–0.13 (–0.42, 0.15)	**–0.08 (–0.10, –0.06)**	–0.01 (–0.03, 0.01)
PA (per 1000 steps/day)	**0.04 (0.02, 0.05)**	**0.02(0.002, 0.04)**	**1.07 (0.43, 1.71)**	**0.53 (–0.01, 1.07)**	**0.08 (0.04, 0.12)**	**0.04 (0.003, 0.07)**
Knee stiffness	0.01 (–0.01, 0.04)	0.01(–0.02, 0.03)	**–1.84 (–2.65, –1.03)**	–0.17 (–0.80, 0.46)	**–0.19 (–0.24, –0.14)**	–0.01 (–0.05, 0.03)
PA (per 1000 steps/day)	**0.04 (0.02, 0.06)**	**0.02(0.001, 0.04)**	**1.07 (0.44, 1.71)**	0.54 (–0.003, 1.08)	**0.08 (0.04, 0.12)**	**0.04 (0.003, 0.07)**
Knee dysfunction	0.001 (–0.002, 0.004)	0.001(–0.002, 0.005)	**–0.28 (–0.39, –0.17)**	**–0.13 (–0.23, –0.04)**	**–0.03 (–0.03, –0.02)**	**–0.01 (–0.01, –0.001)**
PA (per 1000 steps/day)	**0.04 (0.02, 0.06)**	**0.02(0.003, 0.05)**	**0.98 (0.34, 1.62)**	0.50 (–0.05, 1.04)	**0.07 (0.03, 0.11)**	**0.04 (0.001, 0.07)**
Serum 25(OH)D(nmol/L)	**0.005 (0.002, 0.01)**	0.00001(–0.004, 0.004)	**0.13 (0.02, 0.25)**	0.10 (–0.02, 0.21)	**0.01 (0.003, 0.02)**	0.01 (–0.001, 0.01)
PA (per 1000 steps/day)	**0.03 (0.01, 0.05)**	0.02(–0.002, 0.05)	**1.08 (0.41, 1.75)**	0.42 (–0.27, 1.11)	**0.09 (0.05, 0.12)**	0.03 (–0.01, 0.07)

Data in bold indicate statistical significance at $P < 0.05$

Models are adjusted for age, sex, number of chronic conditions (diabetes, rheumatoid arthritis, cardiovascular disease (hypertension, bronchitis/emphysema, or heart attack)), employment status (currently employed vs not currently employed), smoking status, linear time and quadratic time.

†Beta-coefficients expressed as change in 10-year average of the outcome variable per 1 unit increase in the 10-year average predictor variable (25(OH)D, WOMAC and PA). ‡Beta-coefficients expressed as change in outcome variable per 1 unit deviation from the participant's 10-year mean predictor score (25(OH)D, WOMAC and PA)

Chapter 5: Prospective Associations of Low Muscle Mass and Function with 10-year Falls Risk, Incident Fracture and Mortality in Community-dwelling Older Adults

5.1 Abstract

Purpose: To compare the performance of low muscle mass and function with falls risk, incident fracture and mortality over 10 years.

Methods: 1041 participants (50% women; mean age 63±7.5 years) were prospectively followed for 10 years. Falls risk was measured using the Physiological Profile Assessment, fractures were self-reported and mortality was ascertained from the death registry. Appendicular lean mass (ALM) was assessed using dual energy X-ray absorptiometry. Four *anthropometric*: (ALM/height^2, ALM/body mass index, ALM/weight×100, a residuals method of ALM on height and total body fat) and four *performance-based* measures: (handgrip strength, lower-limb muscle strength, upper and lower-limb muscle quality) were examined. Participants in the lowest 20% of the sex-specific distribution for each anthropometric and performance-based measure were classified has having low muscle mass or function. Regression analyses were used to estimate associations between each anthropometric and performance-based measure at baseline and 10-year falls risk, incident fractures and mortality.

Results: Mean falls risk z-score at 10 years was 0.64 (SD 1.12), incident fractures and mortality over 10 years were 16% and 14% respectively. All baseline performance-based measures were significantly associated with higher falls risk score at 10 years. Low handgrip (RR 1.55, 95% CI: 1.09, 2.20) and ALM/body mass index (RR 1.54, 95% CI: 1.14, 2.08) were the only significant predictors of fracture and mortality respectively.

Conclusions: Low handgrip strength, a simple and inexpensive test could be considered in clinical settings for identifying future falls and fractures. ALM/ body mass index could be most suitable in estimating 10-year mortality risk, but requires specialised equipment.

5.2 Introduction

Ageing is associated with changes in body composition including a decline in muscle mass and function [57]. These changes are associated with an increased risk of falls [219], fracture [28, 220], reduced quality of life and death in older people [64]. Age-related decline in muscle strength has been directly attributed to loss of muscle mass [221]. However, recent evidence suggests that age-associated decline in muscle mass and strength occur at different rates and muscle mass may account for as little as 5% of the decrease in muscle strength [61]. Besides, maintaining or improving muscle mass does not prevent age-related decline in muscle strength [57]. Given these potential differences, variations may also exist in the associations between low muscle mass and strength and long-term health outcomes among older people. For example, low muscle strength, but not muscle mass, has been shown to be associated with poor mobility, physical disability [63] and mortality over 6 years [64]. However, few long-term prospective studies have compared the association of muscle mass, strength and muscle quality in predicting health outcomes such as falls, fracture and mortality in community-dwelling older people. Finding the most valid predictor of important clinical endpoints such as falls risk and fracture is crucial in identifying older people at risk. Furthermore, it could also help in the design of intervention trials.

This prospective study aims to describe the association of low muscle mass and function with falls risk, incident fracture and all-cause mortality over 10 years in community-dwelling older adults. We hypothesized that low muscle function may be more relevant in predicting 10-year falls risk, incident fracture and all-cause mortality.

5.3 Data and Methods

5.3.1 Sample and Study Setting

The Tasmanian Older Adult Cohort (TASOAC) study is a prospective, population-based study primarily aimed at examining the causes and progression of osteoarthritis. Participants aged 50 years and above were selected using a sex-stratified random sampling technique from the electoral roll in Southern Tasmania (population 229,000). A total of 1099 adults (response rate = 57%) consented to participate in the study. Participants were excluded if they had any implants that would prevent them from undergoing an MRI or they were living in a nursing home. Participants who consented to participate in the study were invited to attend a clinic at the Menzies Institute for Medical Research, Hobart, Tasmania between March 2002 and September, 2004. They were invited for follow–up clinic assessments at 2.5, 5, and 10 years after the initial clinic assessment. The study was approved by the Tasmanian Health and Medical Research Ethics Committee and written informed consent was obtained from all participants.

5.4 Outcome measures

5.4.1 10 year falls risk

Falls risk at 10 years was assessed using the short form Physiological Profile Assessment (PPA) (Prince of Wales Medical Research Institute, Sydney, Australia), a valid and reliable tool used to identify individuals who are at risk of falls [186]. The PPA assesses five physiological domains (visual contrast sensitivity, reaction time, knee extension strength, proprioception and postural sway on foam) and a standardized falls risk score is calculated for each individual using these five domains.

5.4.2 Fracture

At each study visit participants were asked to list, by location, any fractures they had since their previous visit. Those who experienced at least one fracture between the baseline and 10-year follow-up assessment were coded as '1' (incident fracture.) and those without any fracture were coded '0' (no incident fracture).

5.4.3 Mortality

Mortality over 10 years was ascertained through national and state death registries. Data on mortality was collected until August 2015.

5.5 Baseline measures

5.5.1 Muscle strength measures

Lower-limb muscle strength (kg) was measured simultaneously for both limbs using a dynamometer (TTM Muscular Meter, Tokyo, Japan). Participants stood on the back of a dynamometer platform with their backs against a wall and knee flexed to 115°. A bar was attached to the dynamometer, and participants were instructed to lift the bar using their lower-limbs only to maximum contractile force, whilst maintaining proper head and neck posture. This test assessed the isometric strength of the whole lower-limbs, but predominantly of the quadriceps and hip extensors. Two trials were recorded, with the mean score taken as the criterion value for lower-limbs muscle strength [185]. The intra-class correlation coefficient (ICC) for the first and second trial was 0.95 (95% CI: 0.94–0.96). Handgrip strength (psi) was measured using a pneumatic handheld bulb dynamometer (North Coast^{TM} bulb dynamometer; adult 0-30 psi, model no. 70154). Participants were required to grip the bulb and squeeze as hard as possible. Two trials were recorded for the right and left hand and the mean of grip strength both hands was calculated.

5.5.2 Body composition

Body composition was measured using dual energy X-ray absorptiometry (DXA; Hologic Delphi, Hologic, Waltham USA). Appendicular lean mass (ALM), in kilograms, was calculated as the sum of lean mass in the upper and lower limbs. Weight (kg) was measured using electronic scales (Heine, Dover, USA). Height (cm)

was measured using the Leicester stadiometer (Invicta, Leicester, UK). Body mass index was calculated as weight (kg) divided by height (m) squared.

5.5.3 Measures of low muscle mass and function

Four measures of low muscle mass (anthropometric measures) and four measures of low muscle function (performance-based measures) were considered. *Anthropometric* measures were ALM/height^2 ($ALMHH_{LOW}$) [28], ALM /body mass index [BMI] ($ALMBMI_{LOW}$) [41], ALM/weight multiplied by 100 (ALM_{LOW}) [44] and the residuals of the linear regression of ALM on height and DXA derived total body fat ($ALMR_{LOW}$) [36]. *Performance-based* measures were handgrip strength (HGS_{LOW}), lower-limb muscle strength (LMS_{LOW}) [64] , upper-limb muscle quality (UMQ_{LOW}), and lower-limb muscle quality (LMQ_{LOW}). UMQ_{LOW} was defined as handgrip strength divided by the sum of lean mass in the right and left upper limb and LMQ_{LOW} was defined as lower limb muscle strength divided by the sum of lean mass in the left and right lower limb [63]. Participants in the lowest 20% of the sex-specific distribution for each anthropometric or performance-based measure were classified as having low muscle mass or function [36, 63].

5.6 Data analysis

Linear regression analyses with adjustment for age at baseline were used to estimate the association of low muscle mass and function with 10-year falls risk. Poisson regression was used to estimate incident rate ratios for fracture and mortality over 10 years. Statistical interaction between sex and each measure of muscle mass and

function was assessed by a test of significance of a product term. Data was analysed using Stata version 12.

5.7 Results

One thousand and ninety-nine participants attended the baseline clinics. Of these, 1041 (63 ± 7.5 years; 50% female) completed all anthropometric and muscle function assessments and were included in our analyses. From baseline to 10-year clinic assessments, 489 (47%) participants were lost to follow-up. Compared to participants retained at the 10-year follow-up assessment, participants lost to follow-up were older (64.5±8.0 [range: 51 – 80.9 years] *vs.* 61.4±6.6 [range: 51.1 – 79.9 years], $P<0.001$), had greater number of chronic conditions (1.7±1.5 *vs.* 1.2±1.2, $P<0.001$), poorer baseline ALM (24.1±5.3 *vs.* 24.9±5.3, $P=0.025$), HGS (11.7±3.0 *vs.* 12.4±3.0, $P<0.001$) and LMS (87.8±45.0 *vs.* 96.8±50.5, $P=0.003$) than those who completed the 10 year follow-up, but no sex differences were observed ($P= 0.586$). Baseline characteristics of the participants are shown in Table 5.1. The mean age of the participants at baseline was 63±7.5 (range: 51 – 81 years) and the mean fall risk score was 0.16 ± 0.82, indicating a mild increase in risk of falls. At 10 year follow-up assessment, the mean age was 72.1±6.4 (range: 61.9 – 81.9 years) and 52% were female. The prevalence of low muscle mass or function is shown in Table 5.2. In men, the prevalence ranged from 8% to 19%, 17% to 23%, and 23% to 46% in 50-59 year olds, 60-69 year olds and those aged 70 years and above age, respectively. In women, the prevalence ranged from 13% to 23% in 50-59 year olds, 16% to 21% in 60-69 year olds and from 15% to 44% in those aged 70 years and above. Table 5.3 shows the associations between each anthropometric and performance-based

measures assessed at baseline and 10-year falls risk scores, fracture incidence and mortality over 10 years.

5.7.1 Falls risk

The mean falls risk score at 10 year follow up assessment was 0.64 ± 1.12. There was evidence for positive associations between each of the four performance-based measures at baseline and falls risk score at 10 years. The strongest association was found between baseline LMS_{LOW} and 10-year falls risk score (β=0.60, 95% CI: 0.39-0.81, P<0.001). No associations were found for anthropometric measures, or for any interaction between sex and each measures of muscle mass or function.

5.7.2 Fracture

The incidence of fracture over 10 years was 16.8% (n =147). Evidence for an increased risk of 10-year fracture incidence was found only for HGS_{LOW}. The risk of 10-year fracture incidence associated with HGS_{LOW} was modified by sex (P=0.091): where the association was stronger for women (RR 1.63 95% CI: 1.09-2.42, P=0.017) than men (RR 1.46 95% CI: 0.78-2.71, P=0.234).

5.7.3 Mortality

Over the follow-up period, 14% of the participants (94 men and 51 women) died. Increased risk of 10-year mortality was associated with $ALMBMI_{LOW}$ (RR 1.52 95% CI: 1.13 - 2.06, P=0.006). There was no evidence for an association with any other measures of muscle mass or function or for an interaction between sex and other measures of muscle mass or function.

Table 5.1: Baseline characteristics of participants in the Tasmanian Older Adult Cohort (TASOAC) study (N=1041)

Variables	Mean	SD
Age (years) (range: 51 – 81)	63.0	7.5
Female, n (%)	525	50.4
Height (cm) (range: 141 – 192)	167.1	9.0
Weight (kg) (range: 41.6 – 119.6)	77.8	14.6
BMI (kg/m^2) (range: 17.8 – 52.9)	27.8	4.6
BMI category		
Underweight/Normal, n (%)	319	29.0
Overweight, n (%)	477	43.4
Obese, n (%)	303	27.6
Appendicular lean mass (kg) (range: 14.7 – 39.2)	24.5	5.3
Total body fat (%) (range: 4.4 – 54.5)	33.8	8.0
Handgrip strength (psi†) (range: 3.9 –24.3)	12.1	3.0
Lower-limb muscle strength (kg) (range: 7– 256.5)	92.5	49.1
Falls risk z-score, (range: -2.3– 3.6)	0.17	0.82
Total hip BMD (g/cm^2) (0.97 – 1.70)	0.97	0.15

Values are mean (SD) unless stated otherwise
†psi: pounds per square inch, *BMD* bone mineral density, *SD* standard deviation

Table 5.2: Prevalence of low muscle mass and function at baseline stratified by sex and age (N = 1041)

Low muscle mass / function	Men			Women		
	50-59 years (*n=204*)	60-69 years (*n=200*)	≥70 years (*n=112*)	50-59 years (*n=252*)	60-69 years (*n=173*)	≥ 70 years (*n=100*)
	N (%)	N %	N %	n %	n %	n %
Performance-based measures						
LMQ_{LOW}	25 (12)	46 (23)	33 (30)	40 (16)	32 (19)	34 (34)
UMQ_{LOW}	26 (12)	39 (19)	42 (36)	45 (17)	30 (16)	37 (34)
LMS_{LOW}	16 (8)	41 (20)	55 (46)	34 (13)	33 (17)	48 (44)
HGS_{LOW}	25 (12)	42 (21)	37 (33)	39 (16)	31 (18)	37 (37)
Anthropometric measures						
$ALMHH_{LOW}$	25 (12)	43 (21)	39 (33)	50 (19)	39 (21)	23 (21)
$ALMBMI_{LOW}$	39 (19)	38 (19)	30 (25)	51 (20)	36 (19)	25 (23)
$ALMW_{LOW}$	34 (16)	35 (17)	38 (32)	36 (14)	38 (20)	38 (34)
$ALMR_{LOW}$	35 (17)	45 (22)	27 (23)	59 (23)	36 (19)	17 (15)

UMQ: upper-limb muscle quality (kg/kg) **LMQ**: lower-limb muscle quality; (kg/kg) **LMS**: lower-limb muscle strength (kg) **HGS**: handgrip strength (psi) **ALMHH**: appendicular lean mass (ALM)/height^2 (kg/m^2),) **ALMBMI**: low ALM/body mass index(kg/ kg/m^2) **ALMW**: ALM / weight * 100 (kg/kg) **ALMR**: residual of ALM on height and total body fats (kg)

Table 5.3: Associations between low muscle mass and function at baseline and falls risk at 10-year, incident fractures and mortality over 10 years

Low muscle mass/ function	Cut-point for low muscle mass and function*		Falls risk z-score (*n=551*)	Fracture (*n=841*)	Mortality (*n=1041*)
	Male	Female	β (95% CI)	RR (95% CI)	RR (95% CI)
Performance-based measures					
LMQ_{LOW}	3.85	1.85	**0.41 (0.19, 0.62)**	0.95 (0.63, 1.43)	1.21 (0.89, 1.64)
UMQ_{LOW}	1.08	1.15	**0.29 (0.07, 0.51)**	1.13 (0.78, 1.65)	0.82 (0.59, 1.14)
LMS_{LOW}	69.18	26.40	**0.60 (0.39, 0.81)**	0.93 (0.62, 1.40)	1.03 (0.75, 1.42)
HGS_{LOW}	10.68	7.54	**0.50 (0.27, 0.73)**	**1.55 (1.09, 2.20)**	0.82 (0.60, 1.12)
Anthropometric measures					
$ALMHH_{LOW}$	8.32	6.64	0.03 (–0.19, 0.25)	0.94 (0.63, 1.41)	1.17 (0.85, 1.66)
$ALMBMI_{LOW}$	0.88	0.60	0.08 (–0.15, 0.32)	1.01 (0.67, 1.53)	**1.54 (1.14, 2.08)**
$ALMW_{LOW}$	29.96	24.36	0.13 (–0.10, 0.35)	1.13 (0.77, 1.67)	1.25 (0.91, 1.72)
$ALMR_{LOW}$	–0.87	–1.82	0.13 (–0.80, 0.34)	1.07 (0.73, 1.57)	1.04 (0.73, 1.48)

*: lowest 20%, Data in bold indicate statistical significance at $p<0.05$, All analyses are adjusted for age.

UMQ: upper-limb muscle quality (kg/kg) **LMQ**: lower-limb muscle quality; (kg/kg) **LMS**: lower-limb muscle strength (kg) **HGS**: handgrip strength (psi) **ALMHH**: appendicular lean mass (ALM)/height^2 (kg/m^2),) **ALMBMI**: low ALM/body mass index(kg/ kg/m^2) **ALMW**: ALM / weight * 100 (kg/kg) **ALMR**: residual of ALM on height and total body fats (kg)

5.8 Discussion

This is the first prospective study, to our knowledge, investigating the association between multiple measures of muscle mass and function and falls risk, incident fracture and mortality over 10 years in a large sample of community-dwelling older adults. We found that all performance-based measures at baseline were associated with increased falls risk score at 10 years, but only HGS_{LOW} and $ALMBMI_{LOW}$ were predictive of 10-year fracture incidence and mortality respectively. Importantly, HGS_{LOW} was consistently associated with an increase in falls risk and fracture over 10 years. This finding demonstrates that low handgrip strength alone, a simple and inexpensive procedure, could be considered in clinical settings as a useful screening tool for identifying older adults at risk of falls and fracture. Low muscle mass defined according to ALM adjusted for BMI could be most suitable in estimating 10-year mortality risk in older people, but requires access to specialised equipment.

Increased falls risk score at 10-years was associated with muscle function but not muscle mass. These results are consistent with previous studies [219, 222] and confirm the importance of muscle strength even a decade earlier for predicting falls-risk. Prior studies have also showed that absolute decline in muscle strength and quality, but not muscle mass, are associated with functional limitations and disability – risk factor for falls [63]. Muscle strength decreases at a faster rate than muscle mass [61]. Even when muscle mass appears preserved, there is evidence of a decline in muscle strength [65], which may be attributable to age-related changes in neuromuscular contributors to strength including decreased motor unit recruitment and increased fatty infiltration of muscle. This rapid age-associated decline in strength

may lead to functional limitations at an earlier stage than mass potentially explaining why performance-based measures are superior to anthropometric measures in identifying older adult with higher falls risk over 10 years.

HGS_{LOW} was the only measure that provided evidence for an association with 10-year fracture incidence, and this is consistent with a prior study [135]. Women had a higher prevalence of fracture (21% vs. 11.8% in men) potentially due to higher prevalence of osteoporosis. Therefore, the stronger associations in women could be explained by low muscle strength and low bone density in women leading to falls related fractures. Contrary to our findings, previous studies have established an association between $ALMHH_{LOW}$ and fracture [223-225]. However, these studies were cross-sectional and were conducted among older people admitted to a clinic facility [223-225]. The strongest mechanical loads applied to bones are created by muscle contraction [220]. Hence, low handgrip strength, a reflection of global muscle weakness of the body [135], could be a better indicator of 10-year fracture risk than other measures of low muscle mass or function. Interestingly, despite strong correlation (r= 0.77, $P < 0.001$) between handgrip strength and lower-limb muscle strength in our sample, LMS_{LOW} was not significantly associated with fracture over 10 years. The reason for this observation is not clear.

$ALMBMI_{LOW}$ was the only measure that provided evidence for an association with mortality. Several studies have reported associations between a decline in muscle strength and mortality [43, 64, 226], but conflicting evidence for a decline in muscle mass, with some studies reporting an association [227] and others no association with mortality [64]. Lean muscle mass alone may not be predictive of health outcomes, but

a combination with other anthropometric indices such as BMI may increase sensitivity. BMI is an established risk factor for diseases including cardiovascular disease, cancer, stroke, and is in itself a strong predictor of all-cause mortality [228]. Low BMI is also a strong determinant of transition to sarcopenia [71]. It is possible that low muscle mass defined by combining ALM and BMI was the strongest predictor of mortality because BMI conferred additional risk besides consequences of decline in ALM. Furthermore, low ALM relative to BMI is an indication of high body fat percentage [42], hence, the effect of $ALMBMI_{LOW}$ on mortality may potentially be related to obesity rather than sarcopenia.

HGS_{LOW} was the most consistent predictor, being associated with both falls risk and fracture. The predictive validity of handgrip strength as an important marker of health in older people has previously been established [229]. The mechanisms underlying why this is the case is not entirely certain [229]. Low handgrip strength is potentially a result of chronic conditions such as osteoarthritis, frailty or diabetic neuropathy which are causal risk factors for functional limitation [229]. However, recent findings from a sample of over 130, 000 adults from the Prospective Urban Rural Epidemiology study showed that the association between handgrip strength and cardiovascular diseases, cardiovascular death and all-cause mortality was independent of hypertension, diabetes, prior stroke and other co-morbidities [230]. This suggests that the mechanism may be independent of chronic health conditions, or alternatively may represent sub-clinical disease and/or, lower levels of social, physical or occupational activity, which increase the risk of clinical disease and disability. Further clinical studies incorporating genetics and environmental factors are

warranted to explore why handgrip strength is such a powerful marker of health outcomes [231].

This study has a number of strengths including the 10-year follow-up period, measurement of multiple measures of muscle mass and function and the use of a population-based sample increasing generalizability. A major step in designing an effective intervention is identifying individuals at risk. This prospective population-based study provides evidence for the most appropriate measures of muscle mass and function to identify older people with higher 10-year falls risk, fracture and mortality. However, this study also has a number of limitations. Firstly, there was 19.2% and 47% missing data for incident fracture and falls risk score respectively. This is a major limitation that could lead to bias in our results. Such missing data is not unexpected in a long-term prospective study involving older people. We performed sensitivity analysis for missing data using multiple imputations to assess the robustness of the falls risk and fracture models assuming the data are missing at random. The results of the analyses were similar to the complete case analyses (Table 5.4). Secondly, the incidence of fracture was self-reported and may be subject to recall bias. However, fractures are a major life event and inaccuracy of recall is unlikely [232]. Thirdly, data on the specific cause of death was not available for all the participants, hence, we were unable to perform cause-specific analysis for mortality. Fourthly, grip strength was measured using a pneumatic bulb dynamometer rather than a hydraulic dynamometers (e.g. Jamar), hence cut-points for increased risk of falls and fracture observed in this study may be different for assessments using hydraulic dynamometers. However, previous studies have found high reliability between the two methods [233]. Fifthly, physiological assessment of falls risk rather

than prospective data on actual falls was used in this study and therefore we cannot be certain whether our findings on associations with falls risk score are representative of incident falls. Nevertheless, the physiological approach to the assessment of falls risk used in the study is not subjected to recall bias [234] and the PPA has been shown to have 75% accuracy in predicting multiple falls among older people [187]. On average, our sample was young and overweight. The prevalence of fracture and mortality may have been higher in an 'older' and less overweight population. Lastly, we did not use definitions established for sarcopenia due to our middle-aged and relatively healthy older adult population. For example, previously established cut-points for $ALHMHH_{LOW}$ and $ALMBMI_{LOW,}$ proposed by Baumgartner et al [28] and the Foundation for National Institute of Health (FNIH) sarcopenia project would have only classified 4 (men=4; women=0) and 12 (men=10; women=2) participants respectively as having sarcopenia. In contrast we defined cut-points in the lowest 20% of the sex-specific distribution of each anthropometric and performance-based measure which has previously been used as a diagnostic measure for sarcopenia [36, 63]. Despite this we still found important associations using this method.

In conclusion, findings from this study suggest that low muscle function defined according to low handgrip strength is associated with increased falls risk and incidence of fracture over 10 years. Diagnostic criteria of low muscle mass and function relevant to clinical settings should be readily available, low cost and predictive of future health outcomes [235]. In this respect, defining low muscle function according to low handgrip strength appears to be a promising approach in identifying older people with higher falls and fracture risk over 10 years. Low muscle mass defined according to ALM adjusted for BMI could be most suitable in

estimating 10-year mortality risk in older people, but requires access to specialised equipment.

5.9 Appendix 1: Multiple imputations to account for missing data

At the 10-year clinic assessments, 489 (47%) participants were lost to follow-up. Compared to participants retained at the 10-year follow-up assessment, participants lost to follow-up were older ($P < 0.001$), had more morbidity ($P < 0.001$), and higher baseline falls risk score ($P < 0.001$). Multiple imputations by chained equation was used in the estimation of missing data. Using the known participants' characteristics multiple imputations replaces missing values with plausible values in a way that minimises bias, and helps preserve the sample size [236]. The ability to perform analysis on multiple imputed datasets helps to minimise bias in the parameter estimates. Both the outcomes (excluding mortality) and exposure variables used for analyses in this paper were included in the multiple imputation models. Other variables such as co-morbidity, physical activity, knee pain and dysfunction which were not used in the substantive analysis were also included in the multiple imputation models. Although 3 to 5 imputations are considered adequate to obtain excellent results [237], higher numbers of imputations have been proposed by Graham et. al in order to prevent loss of statistical power [238]. As suggested by Horton and Lipsitz [239], we performed a number of imputations (5, 10, 20 and 50 imputations) and we explored the results using different numbers of imputations. We found consistency in the parameter estimates and results using 50 imputations, as is presented in this paper.

Table 5.4: (supplementary Table) Associations between low muscle mass and function at baseline and falls risk at 10-year, incident fractures and mortality over 10 years (imputed data)

Low muscle mass/ function	Cut-point for low muscle mass and function*		Falls risk z-score (*n=1041*)	Fracture (*n=1041*)
	Male	Female	β (95% CI)	RR (95% CI)
Performance-based definitions				
LMQ_{LOW}	3.85	1.85	**0.44 (0.23, 0.65)**	0.90 (0.54, 1.48)
UMQ_{LOW}	1.08	1.15	**0.33 (0.13, 0.53)**	1.16 (0.73, 1.86)
LMS_{LOW}	69.18	26.40	**0.64 (0.44, 0.83)**	0.82 (0.50, 1.38)
HGS_{LOW}	10.68	7.54	**0.44 (0.23, 0.66)**	**1.72 (1.08, 2.71)**
Anthropometric definitions				
$ALMHH_{LOW}$	8.32	6.64	0.02 (-0.19, 0.23)	0.91 (0.53, 1.55)
$ALMBMI_{LOW}$	0.88	0.60	0.19 (-0.03, 0.41)	1.12 (0.68, 1.84)
$ALMW_{LOW}$	29.96	24.36	0.08 (-0.15, 0.32)	1.28 (0.80, 2.05)
$ALMR_{LOW}$	– 0.87	– 1.82	0.07 (-0.14, 0.28)	1.08 (0.67, 1.75)

*Lowest 20%, Data in bold indicate statistical significance at $p < 0.05$, All analyses are adjusted for age.

UMQ: upper-limb muscle quality (kg/kg) **LMQ**: leg muscle quality; (kg/kg) **LMS**: leg muscle strength (kg) **HGS**: handgrip strength (psi) **ALMHH**: appendicular lean mass (ALM)/height^2 (kg/m^2),) **ALMBMI**: low ALM/body mass index(kg/ kg/m^2) **ALMW**: ALM / weight * 100 (kg/kg) **ALMR**: residual of ALM on height and total body fats (kg)

Chapter 6: Longitudinal Associations between Serum 25-hydroxyvitamin D, Physical Activity, Knee Pain and Dysfunction and Physiological Falls Risk in Community-dwelling Older Adults

6.1 Abstract

Aims: To describe the longitudinal associations between physiological falls risk, and between-person and within-person variability in 25-hydroxyvitamin D (25OHD), physical activity (PA), knee pain and dysfunction in community-dwelling older people.

Methods: Data for 1053 participants (51% women; mean age 63±7.4 years) studied at baseline, 2.5, 5, and 10 years were analysed. Falls risk (Z-score) was measured using the Physiological Profile Assessment. Knee pain and dysfunction were assessed using the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC). Moderate-to-vigorous PA (MVPA) was measured using accelerometer. Linear mixed-effect regression models, with adjustment for confounders, were used to estimate the association between physiological falls risk and between-person and within-person variability in PA, 25OHD and WOMAC score.

Results: Between-person effects showed that 10-year average physiological falls risk was lower in participants who had a higher 10-year average 25OHD (β= -0.005 per nmol/l, 95% CI: -0.008, -0.002), log-MVPA (β= -0.16 per minute, 95% CI: -0.22, -0.10) and lower mean WOMAC score (β=0.005 per-unit score, 95% CI: 0.003, 0.01). Within-person effects showed that a higher physiological falls risk at any time-point was associated with higher than average WOMAC score (β=0.002 per-unit score, 95% CI: 0.0003, 0.004) and lower than average log-MVPA (β= -0.15 per minute, 95% CI: -0.24, -0.06), but not 25OHD, at the same time-point.

Conclusion: Having knee pain and dysfunction above an individual's average increases the risk of falling, whereas, increasing one's own MVPA level further

reduces their risk of falling. The presence of between-person but not within-person associations for 25OHD suggests the former may be confounded by other factors.

6.2 Introduction

Falls among older people are a leading cause of injury-related hospitalization, and account for a substantial amount of preventable healthcare costs [240, 241]. Therefore, reducing falls risk in older people is an important public health concern. Numerous studies have been conducted on falls and their associated risk factors. These studies identified low physical activity levels [145, 242], high knee pain and dysfunction [72, 243], and low serum 25-hydroxyvitamin D (25(OH)D) [149, 244, 245]. However, there is controversy on whether 25(OH)D supplementation reduces falls in community-dwelling older people [152].

Traditionally, analysis has focused on examining how risk factors for falls differ between individuals (*between-person* comparison). As a result, public health efforts have been informed by findings from *between-person* comparisons but less well recognized is how variability in physical activity, 25(OH)D, knee pain and dysfunction over time within the same individual (*within-person* comparison) is associated with falls risk. Examining both the between-person and within-person effects is important as the inferences we make from the between-person effects (for example the magnitude and direction of effects) may not align with those we would make from the within-person effects [73]. Besides, neither can be inferred from the other [205]. Statistical methods, such as multilevel models that properly capture the within-person processes can be used to tell us whether changes within an individual over time relate

to changes in physiological falls risk in that same individual [193]. To our knowledge, there are no published studies that have described the association of within-person variability in physical activity, 25(OH)D, knee pain and dysfunction with physiological falls risk in community-dwelling older people. Therefore, the aim of this study was to describe the association between physiological falls risk and between-person and within-person variability in physical activity, 25(OH)D, knee pain and dysfunction over 10 years in community-dwelling older people.

6.3 Data and Methods

6.3.1 Study population

The Tasmanian Older Adult Cohort (TASOAC) study is a prospective, population-based study primarily aimed at examining the causes and progression of osteoarthritis. Participants aged 50 years and older were selected using sex-stratified random sampling from the electoral roll in Southern Tasmania (population 229,000). A total of 1099 adults (response rate=57%) consented to participate. Participants were excluded if they had any implants that would prevent them from undergoing an MRI or they were living in a nursing home. Participants who consented were invited to attend a clinic at the Menzies Institute for Medical Research, Hobart, Tasmania between March 2002 and September 2004 and follow-up clinic assessments 2.5, 5, and 10 years later. The study was approved by the Southern Tasmanian Health and Medical Research Ethics Committee and written informed consent was obtained from all participants.

6.4 Outcome measure: Physiological falls risk score

Physiological falls risk at baseline, 2.5, 5, and 10 years was assessed using the short form Physiological Profile Assessment (PPA) (Prince of Wales Medical Research Institute, Sydney, Australia), a valid and reliable tool used to identify individuals who are at risk of falls [186]. The PPA assesses five physiological domains (visual contrast sensitivity, reaction time, knee extension strength, proprioception and postural sway on foam) and a standardized falls risk score is calculated for each individual using these five domains.

6.5 Predictor variables

6.5.1 Physical activity

Ambulatory physical activity was assessed at baseline, 2.5 and 5 years. Baseline assessment was measured over seven consecutive days using a pedometer (Omron HJ-003 & HJ-102; Omron Healthcare, Kyoto, Japan) worn on the waist band or belt above their dominant leg. Participants were given a diary in which to record the duration of pedometer use and daily step counts. At 2.5 years follow-up Yamax pedometers (Yamax SW-200; Yamax USA, San Antonio, TX, USA) were given to the majority (98%) of the participants. A strong linear correlation (r=0.88) was found between the estimates of the two types of pedometer, but the Omron brand recorded higher mean steps. Yamax pedometers were used by all participants at 5 years. Baseline and 2.5 years Omron estimates were multiplied by a correction factor of 0.91 to provide comparability between mean estimates for Omron and Yamax pedometers

[191]. Beta coefficients in the regression models were scaled to 1000 steps per day for ease of interpretation.

The intensity of physical activity was assessed in a subset of 637 participants using an accelerometer (ActiGraph GT1M). Participants were instructed to wear the accelerometer for 7 consecutive days, and were provided with a daily diary to record when the accelerometer was worn and when it was removed (for instance, during swimming or showering). Data were included in the analysis if the participants wore the accelerometer for 5 valid days or more; with a valid day being one in which the accelerometer was worn for at least 10 hours. Details about accelerometer data cleaning and the cut-points used for intensity (sedentary, light, moderate, and vigorous) have been described in detail previously [68]. Vigorous physical activity was combined with moderate physical activity because few older adults engaged in vigorous physical activity. Moderate-to-vigorous physical activity (MVPA) was log-transformed as the variable was skewed to the right.

6.5.2 Serum 25-hydroxyvitamin D

Serum 25(OH)D was assessed at baseline, 2.5 and 10-year follow-up. Serum samples from blood drawn from the participants were treated initially with acetonitrile to rapidly extract vitamin-D and other hydroxylated metabolites. Thereafter serum 25(OH)D was assayed using a liquid-phase radioimmunoassay (Immunodiagnostics Systems Ltd), which detects both $25(OH)D_2$ and $25(OH)D_3$. The intra-assay and inter-assay coefficients of variations were 1.8% and 3.3% respectively. Participants had their baseline and follow-up interview at different seasons and as serum 25(OH)D is known to vary with seasons, we de-seasonalised

the 25(OH)D measurement as previously described [246] to account for differences in the time of the year that blood was taken.

6.5.3 Knee pain, stiffness and functional limitation

Knee pain, stiffness and functional limitation were assessed by self-administered questionnaire using the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) at each study visit. WOMAC is a validated and widely used measure of symptoms and disability in patients with osteoarthritis [192]. The three WOMAC sub-scales: knee pain, stiffness and functional limitation were assessed separately with 5, 2 and 17 questions respectively.

6.6 Potential confounders

Age, sex, medical history, including a previous diagnosis of diabetes, rheumatoid arthritis, cardiovascular disease (hypertension, bronchitis/emphysema, or heart attack), as well as smoking history and level of education, was recorded using a questionnaire. Whole and regional body composition of the participants were measured using dual energy X-ray absorptiometry (DXA; Hologic Delphi, Hologic, Waltham USA). Appendicular lean mass and fat mass (sum of lean mass/fat mass in the upper-limbs and lower-limbs) were derived from the DXA scans.

6.7 Data analysis

Measurements for physical activity, 25(OH)D, and knee pain and dysfunction varied across occasions for individuals, and were modelled as time-varying predictors [193, 194]. Time-varying predictors provide two sources of information in longitudinal

analysis; consequently, we decomposed each time-varying predictor into between-person and within-person components. The *between-person* component of the time-varying predictor is an individual's average 25(OH)D, physical activity and WOMAC score across all measurement occasions. The within-person component is the deviation of an individual's measurement at a particular phase of the study from his or her average score across all measurement occasions. As recommended, we first calculated intra-class correlation coefficients (ICCs) for each predictor variable to ensure there was sufficient variance to warrant decomposing the predictors into between-person and within-person effects [193, 198]. The ICC for each predictor variable was calculated using an intercept only model [193, 198]. When ICCs are below 0.05 models can result in biased estimates and convergence difficulties [198]. All ICC of our predictor variables (except for sedentary activity where the ICC was <0.001) were >0.3, suggesting substantial variability in each predictor variable permitting within-person analysis. Due to the low ICC for sedentary activity, we did not model within-person association for sedentary activity and physiological falls risk.

Linear mixed-effect regression models were used to estimate the association between physiological falls risk and between-person and within-person variability in physical activity, 25(OH)D and WOMAC score. The models included a random intercept for individuals and a random coefficient for time to allow for differences in individual trajectories over time. Furthermore, an unstructured covariance matrix with serially correlated residuals was specified to allow for possible correlation between the random intercept and slope. The regression models were adjusted for age at baseline, sex, number of chronic conditions, education, smoking status, time to follow-up,

appendicular lean mass and fat mass. All models were estimated using the maximum likelihood method. Models were selected by comparing the fit of different random and fixed effects of simpler nested models against more complex models using the likelihood ratio test and Akaike Information Criterion [199]. Because different metrics of time can result in different outcomes and interpretation of the results [247], we decided to use, a priori, follow-up time in the regression models with age at baseline since we are interested in modelling intra– and inter-individual variation in falls risk score for every additional year at which the participant entered into the study. Missing data were accommodated in the regression models by using maximum likelihood estimation which estimates means and intercept based on all available data. Data was analysed using Stata version 13 (StataCorp, TX, USA).

6.8 Results

A total of 1053 participants with complete 25(OH)D, WOMAC score and physical activity assessments at baseline were included in the analysis. Of these, 859(82%), 757(72%) and 559(53%) respectively attended the 2.5, 5 and 10 years follow-up assessments. Participants were lost to follow-up because of reasons such as death, institutionalization, withdrawal of consent, joint replacement, and moving interstate or overseas. Participants lost to follow-up were older at baseline (64.7±8.0 *vs.* 61.4±6.6 years, $P<0.001$), had a higher total WOMAC score (21.2±33.9 *vs.* 13.5±24.6, $P<0.001$), lower level of pedometer-determined physical activity (7992±3352 *vs.* 9171±3261 steps/day, $P<0.001$), lower 25(OH)D (50.3±18.0 *vs.* 54.4±19.1 nmol/L, $P<0.001$), higher baseline physiological falls risk score (median= 0.21, interquartile range (IQR): –0.25, 0.79 *vs.* median= –0.01, IQR: –0.52, 0.48;

P<0.001), greater number of chronic conditions (median=1, IQR: 1, 3 vs. median=1 IQR: 0, 1, *P*<0.001) than those who completed the 10 year follow-up, but no sex difference was observed (*P*=0.473).

Baseline characteristics of the participants stratified by the median 10-year average physiological fall risk score are shown in Table 6.1. Participants with a physiological falls risk score above the median value (*i.e.* higher risk of falls) were mostly women (55% *vs.* 45% in men, *P*=0.010) and were older (64.3±7.7 *vs.* 61.4±6.7, *P*<0.001), shorter (166.5±9.0 *vs.* 167.7±8.9, *P*=0.026), weighed less (76.7±15.0 *vs.* 78.9±14.6, *P*=0.020), had lower 25(OH)D (50.7±17.0 *vs.* 54.4±17.0, *P*<0.001) and lower level of physical activity (8246±3393 *vs.* 9075±3274, *P*<0.001). There was no difference in WOMAC scores between participants in the higher and lower median physiological falls risk score. The distribution of physiological falls risk score at each time-points is provided in Figure 6.1.

6.8.1 Disaggregating within- and between-person effects

The estimated between-person and within-person effects of the predictor variables on physiological falls risk score are shown in Table 6.2.

6.8.1.1 Serum 25-hydroxyvitamin-D

Participants with a higher 25(OH)D, on average, had a significantly lower mean physiological falls risk score (β= –0.005; 95% CI –0.008, –0.002). There was no evidence for a within-person 25(OH)D effect on physiological falls risks score (β=0.0001; 95% CI: -0.002, 0.003). However, when the analysis was stratified by 10-year mean level of serum 25(OH)D (*i.e.* optimal [≥50nmol/L] *vs.* sub-optimal

[<50nmol/L]), within-person increase in 25(OH)D was associated with a lower physiological falls risk score in participants with insufficient 25(OH)D but not in those with sufficient 25(OH)D (*P-value* for interaction=0.025) (Figure 6.2).

6.8.1.2 Knee pain and dysfunction

Participants with a higher 10-year average WOMAC global score had a significantly higher 10-year mean physiological falls risk score (β=0.005; 95% CI: 0.003, 0.01) as did those with higher 10-year average WOMAC pain score (β=0.02; 95% CI 0.01, 0.03), knee stiffness (β=0.04; 95% CI 0.02, 0.06), and functional limitation score (β=0.01; 95% CI 0.005, 0.01). Within-person increases in WOMAC global score (β=0.002; 95% CI 0.0003, 0.004), and functional limitation scores (β=0.003; 95% CI 0.001, 0.01) were associated with occasion-specific increases in physiological falls risk score. There was no evidence for a within-person knee pain (β=0.005; 95% CI: –0.003, 0.013) or knee stiffness effect (β=0.004; 95% CI: -0.01, 0.02).

6.8.1.3 Physical activity

Physiological falls risk score was lower in participants with a higher average pedometer-determined steps-per-day (β= –0.02; 95% CI: –0.04, –0.01), higher mean log-MVPA (β=-0.16; 95% CI: -0.22, -0.10) but not sedentary (β= 0.003; 95% CI:-0.004, 0.010) or light physical activity (β= 0.02; 95% CI: -0.05, 0.09). Physiological falls risk was estimated to be lower for individuals when their log-MVPA (β= -0.15; 95% CI: -0.24, -0.06) was higher than their average level of log-MVPA. There was no evidence of an association between within-person variability in light physical activity and pedometer-determined steps-per-day and physiological falls risk score.

Table 6.1: Baseline characteristics of participants in the Tasmanian Older Adult Cohort study, stratified by 10-year median§ physiological fall risk score (N= 1053)

	< Median physiological falls risk score		≥ Median physiological falls risk score		P-value
	Mean	SD	Mean	SD	
Age (years)	61.4	6.7	64.3	7.7	<0.001
Female, n (%)[a]	224	47	315	55	0.010
Height (cm)	167.7	8.9	166.5	9.0	0.026
Weight (kg)	78.9	14.6	76.7	15.0	0.020
25-hydroxyvitamin D (nmol/L)	54.4	17.0	50.7	17.0	<0.001
Appendicular lean mass, Kg	25.0	5.5	23.9	5.2	<0.001
Physical activity (steps/day)	9075	3274	8246	3393	<0.001
Appendicular fat mass, Kg	14.3	4.6	14.7	4.7	0.124
Current smoker, n (%)[a]	224	47	315	55	<0.001
Number of chronic conditions	1.2	1.2	1.7	1.5	<0.001
Currently employed, n (%)[a]	229	55	189	45	<0.001
WOMAC (0 – 216)	14.8	25.1	17.7	29.8	0.092
WOMAC sub-scales					
WOMAC knee pain (0 – 45)	3.4	5.6	3.8	6.5	0.236
Knee stiffness (0 – 18)	1.6	2.5	1.7	2.8	0.533
Functional limitation (0–153)	9.8	17.8	12.2	21.9	0.060

[§]Median physiological falls risk score=0.04

[a] Expressed as percentages

Table 6.2: Linear mixed model estimates of between-person and within-person fixed effects for vitamin-D, physical activity (PA), knee pain and dysfunction and physiological falls risk score (N=1053)

	†*Between–person* effects β (95% CI)	‡*Within–person* effects β (95% CI)
Vitamin-D (nmol/L)	**–0.005 (–0.008, –0.002)**	0.0001 (–0.002, 0.003)
WOMAC total score (unit)	**0.005 (0.003, 0.01)**	**0.002 (0.0003, 0.004)**
WOMAC sub-scales		
WOMAC knee pain	**0.02 (0.01, 0.03)**	0.005 (–0.003, 0.013)
Knee stiffness	**0.04 (0.02, 0.06)**	0.004 (–0.01, 0.02)
Functional limitation	**0.01 (0.005, 0.01)**	**0.003 (0.001, 0.01)**
PA (per 1000 steps/day)	**–0.02 (–0.04, –0.01)**	0.001 (–0.01, 0.02)
Intensity of Physical activity (per minutes/day) (N=632)		
Sedentary activity	–0.0002 (–0.001, 0.0003)	–
Light activity	0.002 (–0.005, 0.01)	–0.001 (–0.01, 0.01)
Log moderate/vigorous activity	**–0.16 (–0.22, –0.10)**	**–0.15 (–0.24, –0.06)**

Data in bold indicate statistical significance at $P<0.05$
Models are adjusted for age at baseline, sex, number of chronic conditions , employment status, appendicular lean mass, fat mass, time to follow-up and smoking status

†: Beta-coefficients expressed as higher/lower 10-year mean physiological falls risk score per 1 unit increase in the 10-year average predictor variable.

‡: Beta-coefficients expressed as higher/lower physiological falls risk score per 1 unit deviation from the participant's 10-year mean predictor score.

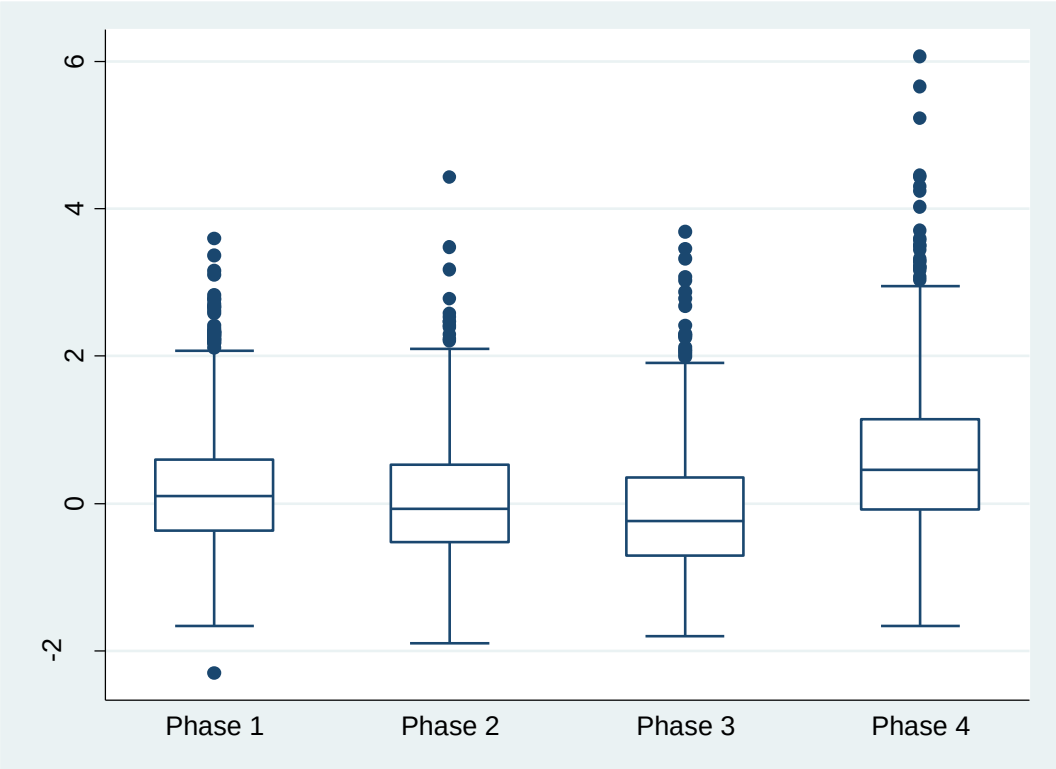

Figure 6.1: Distribution of physiological falls risk score at each time-point

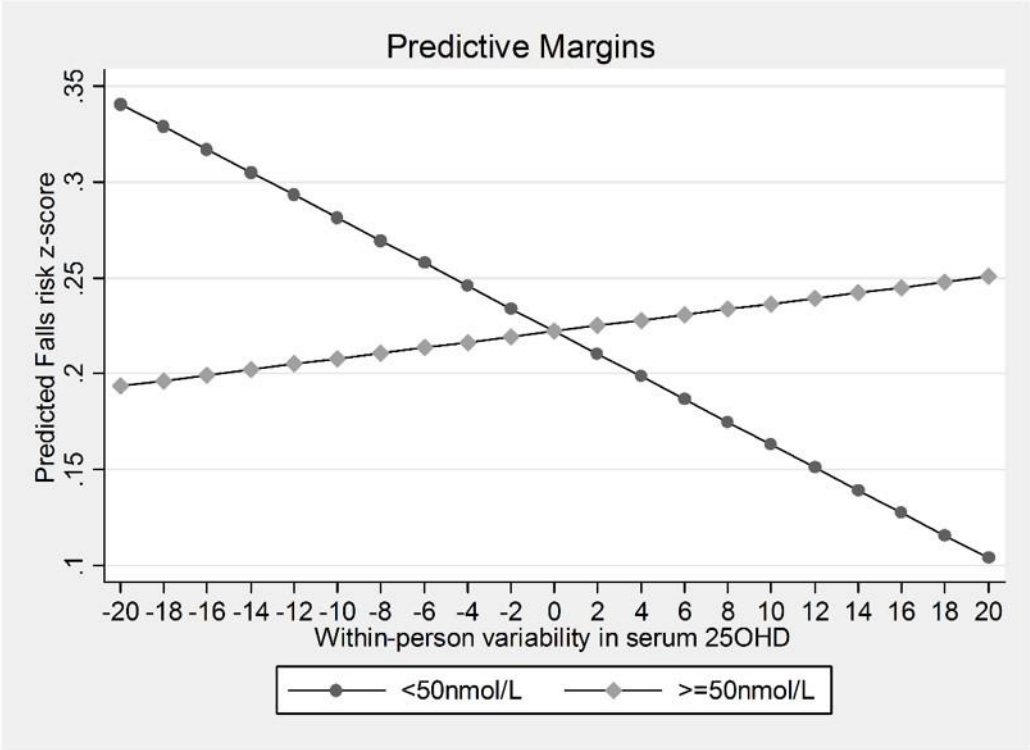

Figure 6.2: Within-person increase in serum 25OHD and falls risk score in older adults with sub-optimal 25OHD (<50 nmol/L) and optimal 25OHD (≥50nmol/L)

6.9 Discussion

To our knowledge, this is the first prospective study to disaggregate within-person and between-person effects of serum 25(OH)D, physical activity, and knee pain and dysfunction on physiological falls risk in community-dwelling older adults. Between-person differences in 25(OH)D, physical activity, and knee pain and dysfunction were associated with physiological falls risk score, such that, average physiological falls risk score was lower in participants who had a higher average 25(OH)D, physical activity and lower mean WOMAC score. Furthermore, within-person variability in WOMAC score was associated with physiological falls risk score, such that physiological falls risk was higher on occasions when WOMAC scores were also higher. This finding has an important clinical implication suggesting that having more knee pain and dysfunction above an individual's average may warrant more attention as falls risk is likely to be higher at this time. In addition, higher than average MVPA also has a protective effect on falls risk.

Between-person but not within-person variability in 25(OH)D was associated with physiological falls risk, suggesting that the between-person associations may be confounded by factors that are held constant in a within-person analysis. However, we did find that a within-person increase in 25(OH)D was associated with a lower physiological falls risk in individuals with sub-optimal (<50nmol/L) but not those with optimal 25(OH)D (≥50nmol/L). The reason for this observation is unclear but may be due to the fact that 25(OH)D was associated with better balance in older adults with sub-optimal, but not in those with optimal 25(OH)D (data not shown). Observational studies have reported a link between low levels of vitamin-D and falls

in older people [148, 149]. However, findings from randomised controlled trials (RCT) and meta-analyses of these trials have been inconsistent, with some showing a benefit and others showing no effects of vitamin-D supplementation in reducing falls in older people [245, 248]. For instance, a meta-analysis of 8 trials testing the efficacy of vitamin-D supplementation on falls in older people showed that supplemental vitamin-D in a dose of 700-1000 IU per day reduced falls risk by 19% [245]. Conversely, supplemental vitamin-D less than 700IU did not reduce the risk of falls, suggesting that low doses of vitamin-D may partly explain why some trials did not find a significant association between vitamin-D supplementation and falls [245]. However, a more recent meta-analysis of 20 trials showed that vitamin D supplementation, with or without calcium does not reduce falls by 15% or more [248]. The differences in the findings from the meta-analyses could be due to the harmful or neutral effects of vitamin-D supplementation reported in more recent trials [248]. An increase in vitamin-D may not help to improve muscle function or physical performance in older adults who are vitamin-D replete [249, 250]. For instance, a 4-year prospective study of 714 adults aged 65 years and older with optimal vitamin-D at baseline revealed no significant association between vitamin-D and physical performance [249]. Our within-person analysis is consistent with studies showing no beneficial effect of 25(OH)D among older people with sufficient vitamin-D.

Interestingly, within-person variability in WOMAC global score and WOMAC functional limitation subscale were associated with physiological falls risk score, such that physiological falls risk was higher on occasions when WOMAC scores were also higher. The effect sizes were smaller than the between-person effect suggesting a less substantive impact. This finding expands upon previous studies by showing that, not

only was falls risk higher in older adults with pain, but that falls risk was also higher on occasions when the older adults had more pain than their 'usual' level of pain. This finding emphasises the importance of within-person analysis in order to understand the impact of intra-individual variability in knee pain and dysfunction on falls risk in community-dwelling older adults. Pain represents a major clinical symptom and there are indications that pain may be undertreated in older people [251]. Clinicians and carers should be more concerned about pain in older adults particularly on occasion when the pain is higher than their 'usual' pain level, as the risk of falling may be higher at this time. Previously we have shown that, in a cross-sectional and prospective study over 5 years, higher knee pain and dysfunction were associated with a higher falls risk [72, 243]. Other studies have also reported a similar association between pain and falls in older adults [252]. Older adults who have knee pain and dysfunction may reduce their mobility in order to avoid discomforts, as a result, they may experience a decline in leg muscle strength and consequently a higher risk of falling. Alternatively, knee pain may also lead to weaker leg muscle strength via reflex muscle inhibition [212], as such, weaker leg muscle strength may lead to poorer balance and a higher falls risk [243]. The significant within-person effect may suggest that on occasion when the participants reported higher knee pain and dysfunction, they also had a greater activity limitation, consequently, they had a weaker leg muscle, poorer balance and a higher falls risk score, or they were perhaps less able to provide a maximal contraction due to actual pain or anticipated pain. Strategies to minimize knee pain and dysfunction may be beneficial for reducing falls in older adults.

Participants with higher average pedometer-determined steps per day and higher MVPA have a significantly lower average physiological falls risk score. Consistent with our findings, several studies have reported a link between a high level of physical activity and lower falls in older people [145, 242]. Although Gill et al [253] reported no beneficial effect of physical activity in the prevention of serious fall injuries others have suggested a U-shaped relationship between physical activity and falls, such that both high and low level of physical activity increased fall risk depending on the older adults' functional status [254]. However, in the Longitudinal Aging Study Amsterdam, Peeters et al [142] found no evidence of a non-linear relationship between physical activity and falls. This finding may be reflected in our own results, suggesting that older adults who engaged in more physical activity, on average, have a lower mean physiological falls risk. Within-person MVPA but not light physical activity or pedometer-determined steps per day was significantly associated with physiological falls risk, indicating that physiological falls risk was lower on occasions when physical activity characterised by a greater level of intensity was also higher. This finding may be related to the additional benefit of MVPA in improving muscle strength, balance and gait parameters in older people [68, 255]. For instance, in a study of people aged 65 years and above, Pau et el showed that although both light and vigorous physical activity help improved static balance, only vigorous physical activity was associated with an improvement in dynamic posture and all the gait patterns considered [255].

This study has a number of strengths including the 10-year follow-up period and the use of objective measures of physical activity which likely increases the accuracy of our estimates. Another key strength of the study was the use of a person-mean

centering analysis approach, allowing us to disentangle the within-person and between-person effects of the predictor variables. This is particularly useful as we observed important differences in the between-person and within-person relationships between 25(OH)D, physical activity and knee pain and dysfunction and physiological falls risk. However, this study also has a number of limitations. Firstly, 48.3% of participants recruited at baseline were lost to follow-up over 10 years. Such missing data is not unexpected in a long-term prospective study involving older people. The missing data were accommodated by using maximum likelihood estimation which uses available data for model estimation, rather than casewise deletion. This is recommended for multilevel data analysis. Secondly, the intensity of physical activity was accessed in a subset of the participants. These participants were found to have fewer chronic conditions and lower knee pain and dysfunction, hence, our findings may be generalisable to healthy older adults' populations. Thirdly, physiological assessment of falls risk rather than prospective data on actual falls was used in this study because actual falls were not collected as part of this study. We cannot be certain whether our findings on associations with falls risk score would be similar for incident falls. However, the physiological approach to the assessment of falls risk is not subject to recall bias [234] and the PPA has been shown to have 75% accuracy in predicting multiple falls among older people [256]. Lastly, to assess potential endogeneity bias we performed a sensitivity analysis by considering time lags between serum 25(OH)D, physical activity, knee pain and dysfunction and falls risk score. There was a consistent relationship between lagged independent variables and physiological falls risk score, suggesting no cause for endogeneity bias.

In conclusion, our findings demonstrate that 10-year average falls risk score was lower in participants who had a higher 10-year mean vitamin-D, physical activity and lower mean WOMAC score. At time-points when the participants had a higher WOMAC score, they also had a higher falls risk. The presence of between-person but not overall within-person associations for 25(OH)D suggests the former may be confounded by other factors. Our finding that within-person variability in MVPA was associated with falls risk supports the clinical recommendation of physical activity for reducing falls risk in older people [257], but it also highlights the additional benefit of increasing one's own MVPA to further reduce falls risk.

Chapter 7: Prospective Associations of Low Muscle Mass and Strength with Health-Related Quality of Life over 10 years in Community-dwelling Older Adults

7.1 Abstract

Aims: This study aims to describe the associations of low muscle mass, handgrip (HGS) and lower-limb muscle strength (LMS) with health-related quality of life (HRQoL) over 10 years in community-dwelling older adults.

Methods: Participants (N=1002; 51% women; mean age 63±7.4 years) were prospectively followed for 10 years. HRQoL was measured using the validated assessment of quality of life (AQoL) instrument. Appendicular lean mass (ALM) was assessed using dual energy X-ray absorptiometry and normalised to body mass index (BMI). HGS and LMS were assessed using dynamometers. Low ALM/BMI (ALM/BMI_{LOW}), LMS (LMS_{LOW}) and HGS (HGS_{LOW}) at baseline were defined as the lowest 20% of the sex-specific distribution for each measure. Linear mixed effect regression models, adjusting for confounders, were used to estimate the association between ALM/BMI_{LOW}, LMS_{LOW}, and HGS_{LOW} at baseline and HRQoL over 10 years.

Results: Participants with LMS_{LOW} (β= –0.061, 95% CI: –0.089, –0.033) and women (β= –0.089, 95% CI: –0.129, –0.049) but not men (β= –0.023, 95% CI: –0.064, 0.019) with HGS_{LOW} had clinically meaningful reductions in HRQoL over 10 years compared to those with normal strength. There was a weaker but statistically significant association between ALM/BMI_{LOW} and 10-year HRQoL (β= –0.038, 95% CI: –0.068, –0.008).

Conclusions: Lower-limb muscle strength and handgrip strength (in women only), which can be easily measured in clinical practice, appear more important than muscle mass for HRQoL. Interventions aimed at reducing the impact of age-related muscle

loss on HRQoL should focus on improving muscle strength rather than just increasing muscle mass.

7.2 Introduction

Age-related decline in skeletal muscle mass and function is associated with health outcomes such as falls risk, fracture, poor mobility and physical disability that could impact older adults' independence and quality of life [63, 200, 201]. However, studies examining the relationship between muscle mass and function and health related quality of life (HRQoL) are sparse and largely cross-sectional [164]. These studies showed that HRQoL, particularly the physical health domain, is lower among older people with low muscle mass and strength [165, 258-261]. However, it is unclear whether cross-sectional associations track over time.

While both muscle mass and strength decrease with age, the two processes do not occur at the same rate and may be the result of dissimilar pathophysiological processes [57, 61, 216]. Prior studies suggest that low muscle mass and strength may have different impacts on health outcomes in older people [63, 167, 201]. Despite these differences, few long-term prospective studies have compared the associations of low muscle mass and strength with HRQoL in community-dwelling older adults. Indeed, clarification of the relationship between low muscle mass and strength and HRQoL of older people may be important in the design of interventions to improve QoL. Therefore, this prospective study aims to describe the association of low muscle mass, handgrip and lower-limb muscle strength assessed at baseline with HRQoL over 10 years in community-dwelling older adults. We hypothesized that low muscle strength may be more closely related to HRQoL than muscle mass.

7.3 Data and Methods

7.3.1 Sample and Study Setting

The Tasmanian Older Adult Cohort (TASOAC) study is a prospective, population-based study primarily aimed at examining the causes and progression of osteoarthritis. Participants aged 50 years and above were selected using a sex-stratified random sampling technique from the electoral roll in Southern Tasmania (population 229,000). A total of 1099 adults (response rate = 57%) consented to participate in the study. Participants were excluded if they had any implants that would prevent them from undergoing an MRI or they were living in a nursing home. Participants who consented to participate in the study were invited to attend a clinic at the Menzies Institute for Medical Research, Hobart, Tasmania between March 2002 and September, 2004. They were invited for follow–up clinic assessments at 2.5, 5, and 10 years after the initial clinic assessment. The study was approved by the Southern Tasmanian Health and Medical Research Ethics Committee and written informed consent was obtained from all participants.

7.4 Outcome measure: Health-related quality of life over 10 years

HRQoL was assessed at baseline, 2.5, 5 and 10 years using the Assessment of Quality of life (AQoL-4D) questionnaire. The AQoL-4D is a validated generic questionnaire designed for the Australian population [188]. The questionnaire consists of 12 items covering four dimensions and each dimension has three items. The four dimensions and their corresponding items are: (1) independent living (self-care, activities of daily living), (2) physical senses (sight, hearing and communication), (3) social

relationships (social isolation, relationship and family role) and (4) psychological wellbeing (sleep, anxiety and pain). The scores for items in each domain were transformed and summed to a life-death utility scale that ranges from 1.00 (full HRQoL) to 0.00 (death-equivalent health state) to –0.04 (health states worse than death) [189, 190]. The minimum important difference in AQoL score for the Australian population is 0.06 [190]. This score provides a measure of the smallest difference in AQoL score that is considered to be of a significant change in the health state of Australians [190].

7.5 Predictor variables

7.5.1 Assessments of low muscle mass and strength at baseline

Lower-limb muscle strength (LMS) was measured to the nearest kilogram simultaneously for both limbs using a dynamometer (TTM Muscular Meter, Tokyo, Japan). Two trials were recorded and the average of the two trials was taken as previously described [185]. The intra-class correlation coefficients of the first and second trial for lower-limb muscle strength assessments was 0.95 (95% CI: 0.94 – 0.96). Hand grip strength (HGS) in pounds per square inch (psi) was measured using a pneumatic handheld bulb dynamometer (North Coast^{TM} bulb dynamometer; adult 0-30 psi, model no. 70154). The mean of the right and left-hand grip strength was calculated for each participant. The intra-class correlation coefficients of the first and second trial for the hand grip strength measurements was 0.96 (95% CI: 0.92 – 0.97). Participants in the lowest 20% of the sex-specific distribution for LMS and HGS at baseline were classified as having low LMS (LMS_{LOW}) and low HGS (HGS_{LOW}) [36, 63].

7.5.2 Body composition assessments at baseline

Whole and regional body composition of the participants were measured using dual energy X-ray absorptiometry (DXA; Hologic Delphi, Hologic, Waltham USA). Appendicular lean mass (ALM), in kilograms, was calculated as the sum of lean mass in the upper and lower limbs. Weight was measured to the nearest 0.1 kilogram using electronic scales (Heine, Dover, USA) with shoes and heavy clothing removed. Height was measured to the nearest 0.1 centimetre using Leicester stadiometer (Invicta, Leicester, UK), with shoes, socks and headgear removed. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. ALM was normalized to BMI as ALM-to-BMI ratio has been shown to be a potential criteria for identifying older adults with clinically relevant weakness [25]. Participants in the lowest 20% of the sex-specific distribution for ALM/BMI at baseline were classified as having low muscle mass (ALM/BMI_{LOW}) [36, 63].

7.6 Potential confounders

Age, sex, medical history, including a previous diagnosis of stroke, diabetes, rheumatoid arthritis, asthma, osteoporosis, cardiovascular disease (hypertension, thrombosis, bronchitis/emphysema, or heart attack) was recorded using a questionnaire. Physical activity was measured over seven consecutive days using a pedometer (Omron HJ-003 & HJ-102; Omron Healthcare, Kyoto, Japan) as previously described [185].

7.7 Data analysis

Means with standard deviations were used to summarize continuous variables, and percentages with participant numbers to describe categorical variables. Linear mixed effect regression analyses with adjustment for age at baseline, sex, self-reported pain and number of chronic conditions were used to estimate the association between low ALM/BMI, HGS and LMS assessed at baseline and AQoL scores over 10 years. Statistical interaction between sex and each muscle parameter was assessed by a test of significance of a (sex × muscle mass or function) product term. Data were analysed using Stata version 12.

7.8 Results

A total of 1002 participants with complete body composition, muscle strength and quality of life assessments at baseline were included in the analysis. Of these, 818 (82%), 722 (72%) and 539 (54%) respectively attended the 2.5, 5 and 10 years follow-up assessments. Participants were lost to follow-up due to death, withdrawal of consent, institutionalization, moving interstate or overseas and having a joint replacement. Participants lost to follow-up were older at baseline (64.5±8.0 *vs.* 62.5±7.3, P=0.001), more commonly female (57% *vs.* 43% in men, P= 0.020), had poorer baseline ALM (23.3±5.3kg *vs.* 24.7±5.3kg, P<0.001), HGS (11.3±2.9psi *vs.* 12.2±3.1psi, P<0.001) and LMS (82.6±45.6kg *vs.* 95.3±49.7kg, P=0.001) than those who completed the 10-year follow-up. No difference in baseline HRQoL (P= 0.323) was observed between participants loss to follow-up (0.76±0.19) and those retained in the study (0.77±0.18). Table 7.1 shows the baseline characteristics of the participants

stratified by low muscle mass and strength. Participants with ALM/BMI_{LOW}, HGS_{LOW} and LMS_{LOW} were older, shorter, had higher levels of knee and foot pain, lower levels of physical activity and greater number of chronic conditions compared to participants with normal muscle mass and strength. Body weight was significantly lower in participants with low HGS and LMS whereas it was higher in those with ALM/BMI_{LOW}. Total body fat was significantly higher only in participants with ALM/BMI_{LOW}. Participants with ALM/BMI_{LOW} had higher hip pain and lower serum 25-hydroxyvitamin D compared to those with normal ALM/BMI, whereas no significant difference in hip pain and serum 25-hydroxyvitamin D was observed between participants with normal and low LMS or HGS. There were no statistical differences in sex and smoking status between participants with low and normal ALM/BMI, LMS and HGS. Figure 7.1 shows the mean predicted HRQoL scores (predictive margin) over time for participants with low and normal ALM/BMI, LMS and HGS. Participants with ALM/BMI_{LOW}, HGS_{LOW} and LMS_{LOW} consistently had a lower HRQoL over time compared to those with normal muscle mass and strength.

The associations between low muscle mass and strength at baseline and HRQoL over 10 years are shown in Table 7.2. Of note, the minimal important difference in the HRQoL score (overall health state utility) is 0.06 for the Australian population [190]. ALM/BMI_{LOW} at baseline was associated with lower HRQoL over 10years (β= –0.038, 95% CI: –0.068, –0.008) with no evidence of an interaction between sex and ALM/BMI_{LOW} (*P*= 0.680). Furthermore, ALM/BMI_{LOW} was associated with a lower independent living (β= –0.018, 95% CI: –0.032, –0.003) and psychological wellbeing (β= –0.026, 95% CI: –0.041, –0.011) component of HRQoL but not with social

relationship (β= –0.012, 95% CI: –0.031, 0.007) or physical senses components (β= –0.004, 95% CI: –0.017, 0.009) of HRQoL.

Participants with LMS_{LOW} at baseline had a clinically meaningful and significantly lower HRQoL over 10 years (β= –0.061, 95% CI: –0.089, –0.033). The association between LMS_{LOW} (β= –0.059, 95% CI: –0.087, –0.032) and HRQoL remained substantially lower after further adjustment for ALM/BMI_{LOW} (β= –0.035, 95% CI: –0.064, –0.006) Table 7.3. There was no evidence for an interaction between sex and LMS_{LOW} (*P*= 0.418) for HRQoL. Furthermore, all four components of HRQoL were significantly lower in participants with LMS_{LOW}: independent living (β= –0.024, 95% CI: –0.038, –0.010), social relationships (β= –0.018, 95% CI: –0.036, –0.0003), physical senses (β= –0.016, 95% CI: –0.028, –0.003) and psychological wellbeing (β= –0.029, 95% CI: –0.044, –0.015).

The association between HGS_{LOW} at baseline and HRQoL over 10 years was modified by sex (*P*=0.008), hence, the results are presented separately for men and women. For men, there was no significant relationship between HGS_{LOW} at baseline and HRQoL or any of the four components of HRQoL (all *P*>0.05). However, among women, HGS_{LOW} at baseline was significantly associated with a clinically meaningful lower level of HRQoL over 10 years (β= –0.089, 95% CI: –0.129, –0.049). Furthermore, women with HGS_{LOW} also had lower scores for the independent living (β= –0.037, 95% CI: –0.058, –0.015), physical senses (β= –0.021, 95% CI: –0.037, –0.005), psychological wellbeing (β= –0.038, 95% CI: –0.060, –0.017) but not social relationships components of HRQoL (β= –0.020, 95% CI: –0.045, 0.005). The association between baseline HGS_{LOW} (β= –0.087, 95% CI: –0.128, –0.047) and

HRQoL over 10 years remained significant after further adjustment for

ALM/BMI_{LOW}, whereas the association with ALM/BMI_{LOW} was not (β= –0.015, 95%

CI: –0.056, 0.026) Table 7.3.

Table 7.1: Baseline characteristics of the participants stratified by ALM/BMI, lower-limb muscle strength, and handgrip strength categories (N=1002)

Variables	ALM/BMI, kg/kg/m^2		Lower-limb muscle strength, kg		Handgrip strength, psi	
	Normal (N=816)	Low (N=186)	Normal (N=803)	Low (N=199)	Normal (N=802)	Low (N=200)
Age (years)	**62.3±7.3**	**65.3±7.7**	**62.1±7.2**	**65.6±7.8**	**61.6±6.9**	**67.6±7.7**
Female n (%)	416(51%)	95(52%)	407(51%)	104(52%)	409(51%)	102 (51%)
Weight (kilogram)	**76.0±14.0**	**84.8±14.6**	**78.3±14.8**	**74.9±12.9**	**78.2±14.7**	**75.4±13.4**
Height (centimetre)	**168.2±8.6**	**162.1±8.8**	**167.6±9.0**	**165.0±8.6**	**167.5±8.9**	**165.3±9.0**
Total body fat (kilogram)	**26.5±7.7**	**34.9±9.1**	28.1±8.7	28.2±8.7	28.0±8.7	28.4±8.6
Energy intake (Kilo Joules/day)	**7784.4±2870.1**	**7269.3±2681.8**	7769.8±2794.4	7361.4±3010.5	7754.2±2594.1	7721.6±2770.6
Physical activity (steps/day)	**9087.3±3301.6**	**7043.1±3177.0**	**8915.3±3329.5**	**7870.8±3423.0**	**8941.9±3366.5**	**7769.3±3237.7**
Smoking n (% yes)	404 (50%)	99 (53%)	405(51%)	98(49%)	411(51%)	92(46%)
Serum 25(OH)D (nmol/L)	**54.1±18.7**	**47.2±16.9**	53.0±18.4	52.1±19.1	52.9±18.7	52.5±18.0
Hip pain (%)	**311(38%)**	**89(48%)**	315(40%)	85(43%)	313(39%)	87(44%)
Knee pain (%)	**344(43%)**	**102(55%)**	**337(42%)**	**109(55%)**	**338(43%)**	**108(54%)**
Foot pain (%)	**278(34%)**	**92(49%)**	**271(34%)**	**99(50%)**	**275(35%)**	**95(48%)**
Number of chronic condition	**1.3±1.3**	**2.0±1.6**	**1.3±1.2**	**1.9±1.6**	**1.3±1.3**	**1.8±1.5**

Data are expressed as mean ± standard deviation unless otherwise indicated;
ALM/BMI: Appendicular lean mass/body mass index; 25(OH)D: 25-hydroxy vitamin D_3; psi: pounds per square inch. To convert psi to kilograms (kg) per centimetre squared multiply by 0.07031.

Table 7.2: Associations between baseline ALM/BMI, HGS, LMS status and health-related quality of life (HRQoL) over 10 years (N=818)

	HRQoL score	Component dimensions of HRQoL			
	(Overall health state utility)	Independent living	Social relationships	Physical senses	Psychological wellbeing
ALM/BMI_{LOW}	**–0.038(–0.068, –0.008)**	**–0.018(–0.032, –0.003)**	–0.012(–0.031, 0.007)	–0.004(–0.017, 0.009)	**–0.026(–0.041, –0.011)**
LMS_{LOW}	**–0.061(–0.089, –0.033)**	**–0.024(–0.038, –0.010)**	**–0.018(–0.036, –0.0003)**	**–0.016(–0.028, –0.003)**	**–0.029(–0.044, –0.015)**
HGS_{LOW} (Men)*	–0.023(–0.064, 0.019)	–0.009(–0.027, 0.009)	–0.021(–0.049, 0.007)	–0.007(–0.028, 0.013)	–0.006(–0.026, 0.014)
HGS_{LOW} (Women)*	**–0.089(–0.129, –0.049)**	**–0.037(–0.058, –0.015)**	–0.020(–0.045, 0.005)	**–0.021(–0.037, –0.005)**	**–0.038(–0.060, –0.017)**

Negative scores indicate poorer health. *Sex interaction existed for HGS, therefore, the results is presented separately for men and women.
Analyses are adjusted for age, sex, physical activity, time to follow-up and number of chronic conditions. Data in bold indicates $P<0.05$.

Note: The HRQoL score ranges from 1.00 (full HRQoL) to 0.00 (death-equivalent health state) to –0.04 (health states worse than death). The minimal important difference in HRQoL score (overall health state utility) for the Australian population is 0.06 [190].

ALM/BMI_{LOW}: Sex specific lowest 20% of appendicular lean mass (ALM)/body mass index [BMI] (kg/ kg/m^2); **LMS_{LOW}**: Sex specific lowest 20% of lower-limb muscle strength (kg); **HGS_{LOW}**: Sex specific lowest 20% of handgrip strength (psi)

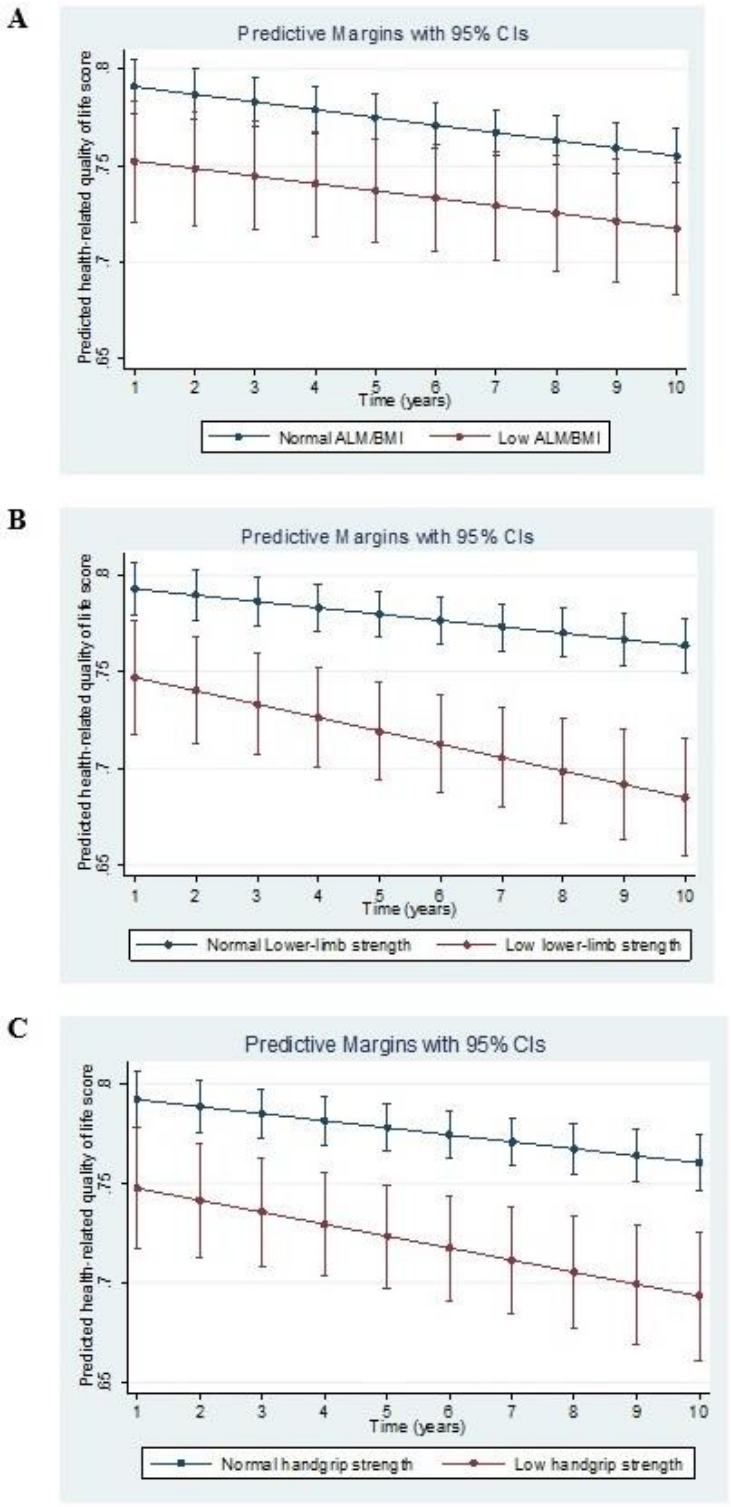

Figure 7.1: Mean HRQoL over time for each ALM/BMI (A), lower-limb muscle strength (B) and handgrip strength (C) categories.

7.9 Discussion

This is the first long-term prospective study, to our knowledge, investigating the association between muscle mass, upper- and lower-limb muscle strength and HRQoL among community-dwelling older adults. Participants with LMS_{LOW} and women with HGS_{LOW} had a clinically meaningful and significantly lower HRQoL over 10 years compared to those with normal strength. The association between ALM/BMI_{LOW} and HRQoL over 10 years was weaker and ALM/BMI_{LOW} did not affect the association between handgrip or lower-limb muscle strength and HRQoL. This demonstrates that muscle strength, which is closely related to physical performance and easy to measure in clinical practice, is a more important predictor of long-term quality of life in community-dwelling older adults than muscle mass, suggesting that interventions aimed at reducing the impact of age-related muscle loss on HRQoL might be better focused on improving muscle strength rather than just increasing muscle mass.

In older adults, both men and women with lower muscle mass, lower-limb muscle strength and women but not men with lower handgrip strength at baseline had lower HRQoL over 10 years. Interestingly, a greater and more clinically meaningful difference (approaching or exceeding 0.06) in HRQoL [190] was observed for older adults with LMS_{LOW} and women with HGS_{LOW} than in those with low muscle mass, the latter effect being around 40 – 60% the magnitude of the former two. One reason for this could be that age-associated loss of muscle strength occurs at a faster rate than loss of muscle mass [57]. A rapid loss of muscle strength can result in early onset of functional impairments, physical inactivity and poor social engagement that could

have a larger impact on HRQoL. Contrary to our findings, a recent 3-year prospective study suggested that muscle mass, not muscle strength, was significantly associated HRQoL [262]. However, this study was limited by its very small sample size (n=26) and because QoL was assessed using only the physical components of 36 item short-form survey (SF-36) rather than the combined physical and mental components. Indeed, physical components of SF-36 correlates poorly with muscle strength and this measure alone may not be a suitable outcome measure in musculoskeletal studies [260]. Consistent with our findings, several studies have documented the clinical utility of muscle strength as a better predictor of health and HRQoL in older adults [62, 260]. This, combined with the fact that low muscle mass did not affect the clinically meaningful decrease in HRQoL in individuals with low muscle strength, suggest that interventions aimed at reducing the impact of age-related muscle loss on HRQoL should focus on improving muscle strength rather than just increasing muscle mass.

Women with HGS_{LOW} had a lower HRQoL over 10 years, while no significant association was found in men. The reason for this observation is unclear, nonetheless, this finding is consistent with prior studies which suggest that maintenance of HGS appears to be more important in reducing detrimental health outcomes in women compared to men [263]. One possible explanation is that women generally have a lower upper-limb muscle strength than men, hence, any loss of upper-limb strength in women is more likely to result in difficulty performing tasks required to maintain function [34]. Potentially this contributes to an increased likelihood of loss of independence and poorer HRQoL in women.

Participants with ALM/BMI_{LOW}, LMS_{LOW}, and women with HGS_{LOW} had lower scores on the independent living component of HRQoL. This demonstrates the importance of preserving muscle mass and strength in order to perform tasks associated with maintaining independent living over a decade. A requirement for independent living in old age is the ability to perform (instrumental) activities of daily living (ADL/IADL) with no difficulty [264]. In several studies, older adults with advanced muscle loss have had a reduced capacity to perform ADLs as well as an increased need for health support services and subsequent institutionalisation [63, 200, 264]. Public health initiatives that help older adults maintain muscle mass and strength will be important to decrease dependency in later life.

Social relationship component of HRQoL was significantly lower only in individuals with $LMS_{LOW,}$ suggesting that lower extremity muscle strength could be important in maintaining an interpersonal relationship with friends and family over the long-term. Contrary to our findings in this community-dwelling population, previous cross-sectional studies among pre-frail and frail older adults have reported no significant association between muscle strength and social participation [265, 266]. It may be that poor lower extremity muscle strength in independent living older adults could result in greater social isolation than in frailer adults with complex medical conditions and are likely to receive to health supports. This could occur via impairment in mobility, as a reduction in mobility is associated with a decline in physical function [267]. Interestingly, physical senses domain of HRQoL was lower in older adults with LMS_{LOW} and women with HGS_{LOW} whereas no associations was observed for ALM/BMI_{LOW}. Low muscle strength is not likely to be a direct cause of poorer physical senses, rather it could lead to the development of some chronic diseases

which affect physical senses. Furthermore, low muscle strength may also be a marker of pre-existing or current chronic conditions (such as diabetes) affecting physical senses like visual function.

Interestingly, the psychological wellbeing component of HRQoL was lower in older adults with ALM/BMI$_{LOW}$, LMS$_{LOW}$, and women with HGS$_{LOW}$. This is consistent with prior studies reporting poorer psychological health in older adults with low muscle mass and strength, although the mechanism underlying the association between age-related muscle loss and psychological wellbeing is not entirely clear [261, 268-271]. Potentially loss of independent living skills associated with low muscle mass and strength could have physical and emotional impacts on older adults, and could contribute to poorer psychological wellbeing. For instance, a recent systematic review and meta-analysis of 15 observational studies reported a significantly higher odds of depression in older adults with sarcopenia [270]. Muscle function may be related to psychological wellbeing because they both have a central nervous system involvement and muscle weakness may be an early indicator of age-related decline in central nervous system that is manifested in poor mental health [268]. Indeed, resistance exercises have been shown to lead to an improvement of, and prevention of decline in mental health, in addition to improvement in muscle strength suggesting a link between the two processes [272, 273]. Further clinical studies incorporating brain morphology and neuroplasticity are warranted to determine the physiological mechanisms through which low muscle mass and strength may be related to poorer psychological wellbeing [274].

The strengths of this study includes the 10-year follow-up period and the use of a population-based sample which increases its generalizability. In addition, muscle mass was assessed using DXA, a valid and accurate tool for assessing muscle mass. However, this study has a number of limitations. Forty-six percent of the participants were lost to follow-up over 10 years. Such missing data is not unexpected in a long-term prospective study involving older people. The missing data were accommodated in the linear mixed effect models by using maximum likelihood estimation which estimates means and intercepts based on all available data. This minimize bias and increase power as participants with missing follow-up data were retained in the analysis. HRQoL was assessed using a generic questionnaire rather than a disease-specific HRQoL measure such as the sarcopenia and quality of Life (SARQoL) questionnaire. Unlike SARQoL, AQoL was not originally designed to assess the impact of age-related loss of muscle mass and function, nonetheless, some of the items (for instance, difficulty with ADL, mobility and pain) assessed in SarQoL are also captured in AQoL. AQoL is a commonly used tool specifically designed for the Australian population demonstrating both validity and reproducibility [190].

In conclusion, lower-limb muscle strength and handgrip strength (in women only) were a better predictor of HRQoL over 10 years compared to muscle mass. In this respect, measuring muscle strength in clinical practice appears to be a promising approach to identify older adults who are at risk of having a considerable decline in HRQoL as they age. As age-related decline in muscle strength is amenable to interventions, resistance exercise training aimed at improving muscle strength may have a beneficial impact on long-term HRQoL. Interventions aimed at reducing the

impact of age-related muscle loss on HRQoL should focus on improving muscle strength rather than just increasing muscle mass.

Table 7.3: Supplementary Table: Associations of baseline LMS status and HGS (women only) with health-related quality of life (HRQoL) over 10 years, with additional adjustment for baseline ALM/BMI (N=818)

	HRQoL score	Component dimensions of HRQoL			
	(Overall health state utility)	Independent living	Social relationships	Physical senses	Psychological wellbeing
LMS_{LOW}	**–0.059(–0.087, –0.032)**	**–0.023(–0.037, –0.010)**	–0.018(–0.037, 0.0002)	**–0.016(–0.028, –0.003)**	**–0.028(–0.042, –0.014)**
ALM/BMI_{LOW}	**–0.035(–0.064, –0.006)**	**–0.016(–0.031, –0.002)**	–0.011(–0.030, 0.008)	–0.003(–0.016, 0.010)	**–0.024(–0.040, –0.009)**
HGS_{LOW} (Women)	**–0.087(–0.128, –0.047)**	**–0.036(–0.057, –0.014)**	–0.020(–0.045, 0.006)	**–0.021(–0.038, –0.005)**	**–0.036(–0.058, –0.014)**
ALM/BMI_{LOW}	–0.015(–0.056, 0.026)	–0.007(–0.029, 0.014)	–0.004(–0.030, 0.022)	–0.002(–0.014, 0.018)	–0.018(–0.040, 0.004)

Negative scores indicate poorer health. Analyses are adjusted for age, sex, physical activity, time to follow-up and number of chronic conditions. Data in bold indicates $P<0.05$.

Note: The HRQoL score ranges from 1.00 (full HRQoL) to 0.00 (death-equivalent health state) to –0.04 (health states worse than death). The minimal important difference in HRQoL score (overall health state utility) for the Australian population is 0.06 [190].

ALM/BMI_{LOW}: Sex specific lowest 20% of appendicular lean mass (ALM)/body mass index [BMI] (kg/ kg/m^2); **LMS_{LOW}**: Sex specific lowest 20% of lower-limb muscle strength (kg); **HGS_{LOW}**: Sex specific lowest 20% of handgrip strength (psi)

Chapter 8: Prospective Associations of Osteosarcopenia and Osteodynapenia with Incident Fracture and Mortality over 10 years in Community-dwelling Older Adults

8.1 Abstract

Aim: To determine whether older adults with low muscle mass (sarcopenia) and strength (dynapenia), in the presence of osteoporosis/osteopenia, have an increased risk of fracture and mortality over 10 years, compared to those with low muscle or low bone mass alone or with neither condition.

Methods: 1032 participants (52% women; mean age 62.9±7.4 years) were studied at baseline, 2.5, 5 and 10 years. Mortality was ascertained from the death registry and fractures were self-reported. Baseline appendicular lean mass (ALM) was assessed using dual-energy X-ray absorptiometry and normalised to body mass index (BMI). Hand grip strength (HGS) was assessed by dynamometer. Osteosarcopenia and osteodynapenia were defined as having T-scores of the total hip and/or lumbar spine bone mineral density (BMD) < –1 combined with being in the lowest 20% of the sex-specific distribution for ALM/BMI or HGS respectively.

Results: Incident fracture risk was significanlty higher in participants who were osteodynapenic (RR=2.07, 95% CI: 1.26–3.39), dynapenic alone (RR=1.74, 95% CI: 1.05–2.87), and osteopenic alone (RR=1.63, 95% CI: 1.15–2.31), compared to those without dynapenia or osteopenia. Mortality risk was significantly higher only in participants with osteosarcopenia (RR=1.49, 95% CI: 1.01–2.21) compared to those without sarcopenia or osteopenia. However, osteosarcopenia and osteodynapenia did not lead to a significantly greater fracture or mortality risk compared to having these conditions on their own.

Conclusion: Osteopenia combined with low muscle mass or strength does not significantly increase the risk of fracture or mortality compared to having osteopenia or sarcopenia/dynapenia alone, suggesting that combined assessments may not add additional risk for fracture and mortality.

8.2 Introduction

Ageing is associated with changes in body composition including decreases in muscle mass, strength and bone mass, with declines in each occurring at a different rate [275, 276]. Loss of muscle mass and loss of bone mass (osteopenia/osteoporosis) are closely interconnected, however, both have been considered independently as risk factors for falls, fracture and mortality in older people [175]. Historically, the interconnection between muscle and bone mass has been thought to be through the mechanostat model which postulates that a decrease in muscle function would result in a decline in mechanical loading on bone and consequently results in a decrease in bone mass [277]. However, recent evidence suggests that, beyond the mechanostat model, there is a biochemical and metabolic interconnection between muscle and bone [180]. Indeed, a significant proportion of older people with low muscle function also experience osteopenia/osteoporosis [180, 278]. Due to the close interconnection between bone and muscle tissue, the simultaneous occurrence of osteopenia/osteoporosis and low muscle mass/strength could significantly increase the risk of fracture and mortality compared to low muscle mass/strength or osteopenia/osteoporosis alone.

Previous cross-sectional studies showed that older adults with combined low muscle and bone mass experienced higher falls, fracture and poorer quality of life compared

to those without low muscle or low bone mass [278]. However, limited long-term prospective studies have described the association between the combination of low muscle and bone mass with fracture and mortality in older people [134]. It is also unclear whether low bone mass when combined with low muscle mass has a different impact on fracture and mortality than when combined with low muscle strength. This is particularly important to investigate because muscle strength is associated with functional declines in older people independent of muscle mass [279]. The aim of the present study was to determine whether older adults with low muscle mass (sarcopenia) and strength (dynapenia), in the presence of osteoporosis/osteopenia, have an increased risk of fracture and mortality over 10 years, compared to those with low muscle or low bone mass alone or with neither condition. We hypothesised that fracture and mortality risk over 10 years will be significantly higher in older people with combined low muscle and bone quality compared to individuals with low muscle or low bone mass alone and those with neither condition.

8.3 Data and Methods

8.3.1 Sample and Study Setting

The Tasmanian Older Adult Cohort (TASOAC) study is a prospective, population-based study primarily aimed at examining the causes and progression of osteoarthritis. Participants aged 50 years and above were selected using sex-stratified random sampling from the electoral roll in Southern Tasmania (population 229,000). A total of 1099 adults (response rate = 57%) consented to participate in the study and were invited to attend a clinic at the Menzies Institute for Medical Research, Hobart, Tasmania between March 2002 and September, 2004. They were invited for follow–

up clinic assessments at 2.5, 5, and 10 years after the initial clinic assessment. The study was approved by the Tasmanian Health and Medical Research Ethics Committee and written informed consent was obtained from all participants.

8.4 Outcome measures

8.4.1 Fracture

At each study visit participants were asked to list, by site, any fractures they had since their previous visit. Those who experienced at least one fracture between the baseline and 10-year follow-up assessment were coded as '1' (incident fracture.) and those without any fracture were coded '0' (no incident fracture).

8.4.2 Mortality

Mortality over 10 years was ascertained through national and state death registries.

8.5 Baseline measures

8.5.1 Anthropometrics

Weight was measured to the nearest 0.1 kilogram (kg) using electronic scales (Heine, Dover, USA) with shoes and heavy clothing removed. Height was measured to the nearest 0.1 centimetre using Leicester stadiometer (Invicta, Leicester, UK), with shoes, socks and headgear removed. Body mass index (BMI) was calculated as weight (kg) divided by height (metre) squared.

8.5.2 Body composition and BMD measures

Lean mass, fat mass, right hip and lumbar spine bone mineral density (BMD) were measured using dual-energy X-ray absorptiometry (DXA; Hologic Delphi, Hologic, Waltham USA). Appendicular lean mass (ALM) calculated as the sum of lean mass in the upper and lower limbs was normalised to body mass index [BMI] (ALM/BMI) [41].

8.5.3 Muscle strength

Handgrip strength in pounds per square inch (psi) was measured using a pneumatic handheld bulb dynamometer (North Coast^{TM} bulb dynamometer; adult 0-30 psi, model no. 70154). The mean of the right and left handgrip strength was calculated for each participant. The intra-class correlation coefficients of the first and second trial for handgrip strength measurements was 0.96 (95% CI: 0.92 – 0.97).

8.5.4 Operational definitions of osteosarcopenia and osteodynapenia

Osteopenia was defined as a T-scores of the total hip and/or lumbar spine of less than –1 [184, 280, 281]. Sarcopenia and dynapenia were defined as being in the lowest 20% of the sex-specific distribution of muscle mass and strength respectively of our study sample at baseline [36, 63]. Participants were classified into one of the following four categories based on osteopenic and sarcopenic status: (1) non-sarcopenic, non-osteopenic; (2) sarcopenic non-osteopenic; (3) osteopenic non-sarcopenic; (4) osteosarcopenic. A similar classification was made based on osteopenic and dynapenic status: (1) non-osteopenic, non-dynapenic; (2) dynapenic non-osteopenic; (3) osteopenic non-dynapenic; (4) osteodynapenic.

8.6 Potential confounders

Physical activity was measured over seven consecutive days using a pedometer (Omron HJ-003 & HJ-102; Omron Healthcare, Kyoto, Japan) as previously described [185]. Serum 25-hydroxyvitamin D [25(OH)D] was assayed using a liquid-phase radioimmunoassay (Immunodiagnostics Systems Ltd), which detects both 25(OH)D2 and 25(OH)D3. The intra-assay and inter-assay coefficients of variation were 1.8% and 3.3% respectively. Serum 25(OH)D was de-seasonalised as previously described [15] to account for differences in the time of the year that blood was taken. Age, sex, medical history, including a previous diagnosis of diabetes, rheumatoid arthritis, cardiovascular disease (hypertension, bronchitis/emphysema, or heart attack) were recorded using a questionnaire. Falls risk was assessed using the short form Physiological Profile Assessment (PPA) (Prince of Wales Medical Research Institute, Sydney, Australia), a valid and reliable tool used to identify individuals who are at risk of falls [186].

8.7 Data analysis

Categorical and continuous variables were compared across categories of osteopenia/sarcopenia and osteopenia/dynapenia using Chi-square tests and one-way ANOVA, respectively. Poisson regression was used to estimate the relative risk (RR) for fracture and mortality over 10 years in unadjusted and adjusted analysis. The fracture models were adjusted for age, sex, physical activity (steps/day) and 25-hydroxyvitamin-D. The mortality models were adjusted for age, sex, physical activity (steps/day) and number of chronic conditions. We assessed statistical interaction

between sex and osteopenic/sarcopenic and osteopenic/dynapenic status. Additionally, we modelled fracture and mortality using continuous (hip BMD) and muscle measures (muscle mass (ALM/BMI) and strength (HGS)) in both univariable and multivariable models. Hip BMD, HGS and ALM/BMI were standardised for comparison and the relative risk of fracture and mortality were reported as per standard deviation (SD) decrease in hip BMD and per SD increase in HGS or ALM/BMI. We assessed the robustness of our models to missing data using inverse probability weighting. Data were analyzed using Stata version 13 (StataCorp, TX, USA).

8.8 Results

A total of 1032 participants (63 ± 7.4 years; 52% female) with complete body composition and muscle strength assessments at baseline were included in the analysis. Table 8.1 presents the baseline characteristics of the participants stratified according to osteopenic, sarcopenic and dynapenic status. Both osteosarcopenic and osteodynapenic participants were older, shorter, had lower ALM, and engaged in lower levels of physical activity compared to non-sarcopenic non-osteopenic and non-dynapenic non-osteopenic participants. There were a higher proportion of women in the osteodynapenic group compared to non-dynapenic non-osteopenic participants. The proportion of women in the osteopenic non-sarcopenic group was significantly higher than those in the non-sarcopenic non-osteopenic category. BMI and total body fat mass were significantly higher in participants with osteosarcopenia compared to those who were non-sarcopenic non-osteopenic. BMI but not total body fat mass was significantly lower in participants with osteodynapenia compared to those who were

non-dynapenic non-osteopenic. Smoking status did not differ across sarcopenic, osteopenic and dynapenic categories. Participants with osteosarcopenia had a greater number of chronic conditions and lower levels of serum 25(OH)D compared to non-sarcopenic non-osteopenic participants whereas no significant differences in serum 25(OH)D or number of chronic conditions was observed between osteodynapenic and non-dynapenic non-osteopenic participants. Falls risk score did not differ across sarcopenic/osteopenic categories whereas it was significantly higher among participants with osteodynapenia compared to those who were non-dynapenic non-osteopenic.

Incident fracture and mortality over 10 years were 17% and 15% respectively. Figure 8.1 shows the incidence of fracture over 10 years stratified according to osteopenic, sarcopenic and dynapenic status. Incident fractures were more common in participants who were osteosarcopenic (21%) and osteopenic non-sarcopenic (21.5%) compared to those who were sarcopenic non-osteopenic (13%) and non-sarcopenic non-osteopenic (13.5%). Fracture was also more common among participants who were osteodynapenic (25.4%), osteopenic non-dynapenic (20.4%) and dynapenic non-osteopenic (19.5%) compared to those who were non-dynapenic non-osteopenic (12%). The interaction between osteopenia and sarcopenia (P=0.666) or dynapenia (P=0.763) was not statistically significant.

Figure 8.2 shows the incidence of mortality over 10 years stratified according to osteopenic, sarcopenic and dynapenic status. Mortality was higher in participants who were osteosarcopenic (27.9%), and sarcopenic non-osteopenic (23.2%) compared to those who were osteopenic non-sarcopenic (15.3%) and non-sarcopenic non-

osteopenic (11.3%). Mortality was also higher in participants who were osteodynapenic (22%) and dynapenic non-osteopenic (21.6%) compared to those who were osteopenic non-dynapenic (16.4%) and non-dynapenic non-osteopenic (11.5%). The interaction between osteopenia and sarcopenia (*P*=0.002) was statistically significant whereas no statistical interaction was observed between osteopenia and dynapenia (*P*=0.550)

8.8.1 Associations of Osteosarcopenia and Osteodynapenia with Incident Fracture

Table 8.2 shows the risk ratios for self-reported fracture over 10 years according to osteopenic, sarcopenic, and dynapenic categories. Fracture risk was significantly higher among participants who were osteopenic non-sarcopenic (RR=1.50, 95% CI: 1.07, 2.10) but not among those who were osteosarcopenic (RR=1.48, 95% CI: 0.83, 2.64) or sarcopenic non-osteopenic (RR=0.97, 95% CI: 0.52, 1.81), compared to non-sarcopenic non-osteopenic participants. Osteosarcopenia did not lead to a significantly greater risk of fracture compared to those with sarcopenia alone (*P*= 0.255) or osteopenia alone (*P*=0.964).

Fracture risk was significantly higher in participants who were osteodynapenic (RR=2.07, 95% CI: 1.26–3.39), dynapenic non-osteopenic (RR=1.74, 95% CI: 1.05, 2.87), and osteopenic non-dynapenic (RR=1.63, 95% CI: 1.15, 2.31), compared to those without dynapenia or osteopenia. Osteodynapenia did not lead to a significantly greater risk of fracture compared to those with dynapenia alone (*P*= 0.561) or osteopenia alone (*P*= 0.311).

There was no significant sex interaction with regards to the association between fracture risk and sarcopenic/osteopenic categories (P=0.889) or dynapenic/osteopenic categories (P=0.749). Table 8.3 shows the RR for fracture with muscle mass (ALM/BMI), strength (HGS) and hip BMD used as continuous variables. Every 1 SD decrease in hip BMD resulted in a 32% increase in fracture risk (RR=1.32, 95% CI: 1.09, 1.61), whereas no significant association was observed between ALM/BMI and fracture (RR=0.96 per 1 SD increase, 95% CI: 0.73, 1.27). Furthermore, there was no evidence for an association between HGS (RR=0.81 per 1 SD increase, 95% CI: 0.63, 1.03) and fracture risk; whereas, every 1 SD decrease in hip BMD resulted in a 31% increase in fracture risk (RR=1.31, 95% CI: 1.08, 1.58).

8.8.2 Associations of Osteosarcopenia and Osteodynapenia with Mortality

Table 8.4 shows the incident rate ratios for mortality over 10 years according to osteopenic, sarcopenic, and dynapenic categories. Mortality risk was significantly higher among participants who were osteosarcopenic (RR=1.49, 95% CI: 1.01, 2.21) but not among those who were osteopenic non-sarcopenic (RR=1.27, 95% CI: 0.92, 1.76) or sarcopenic non-osteopenic participants (RR=1.30, 95% CI: 0.88, 1.91), compared to those participants who were non-sarcopenic non-osteopenic. The combination of osteosarcopenia did not lead to a significantly greater risk of fracture compared to those with sarcopenia alone (P=0.529) or osteopenia alone (P=0.418).

There was no evidence for increased risk of mortality for participants who were osteodynapenic (RR=1.03, 95% CI: 0.68, 1.57), dynapenic non-osteopenic (RR=0.91, 95% CI: 0.62, 1.34) or osteopenic non-dynapenic (RR=1.27, 95% CI: 0.93, 1.72) compared to those who were non-dynapenic non-osteopenic. The combination of

osteodynapenia did not lead to a significantly greater risk of fracture compared to those with dynapenia alone (P=0.602) or osteopenia alone (P=0.318).

There was no significant sex interaction with regards to the association between mortality risk and sarcopenic and osteopenic categories (P=0.555) or dynapenic and osteopenic status (P= 0.514). Table 8.5 shows the relative risk for mortality with muscle mass (ALM/BMI), strength (HGS) and hip BMD used as continous variables. As a continuous variable, there was no evidence for an association among hip BMD, ALM/BMI, HGS and mortality in the multivariable models.

Table 8.1: Baseline descriptive characteristics according to categories of sarcopenia, dynapenia and osteopenia

Variables	Non-sarcopenic, Non-osteopenic *N = 471*	Osteopenic non-sarcopenic *N =367*	Sarcopenic non-osteopenic *N =108*	Osteosarcopenic *N =86*	Non-dynapenic, Non-osteopenic *N =468*	Osteopenic non-dynapenic *N =353*	Dynapenic non-osteopenic *N =111*	Osteodynapenic *N =100*
Age (years)	61.3 ± 6.9	63.7 ± 7.6[a]	64.5 ± 7.8[a]	66.5 ± 7.3[a]	60.9 ± 6.6	62.9 ± 7.2[b]	66.3 ± 7.9[b]	68.8 ± 7.0[b]
Female, (%)*	219 (47%)	213 (58%)[a]	50 (46%)	50 (58%)	225 (48%)	200 (57%)	44 (40%)	63 (63%)[b]
Weight (Kg)	80.1 ± 13.7	70.5 ± 12.4[a]	88.2 ± 14.3[a]	80.1 ± 14.6	81.9 ± 14.5	72.8 ± 13.6[b]	80.2 ± 12.8[b]	70.7 ± 12.5[b]
Height (cm)	169.5 ± 8.5	166.4 ± 8.5[a]	164.1 ± 8.4[a]	159.6 ± 8.7[a]	168.8 ± 8.8	165.7 ± 8.9[b]	167.6 ± 8.4	163.1 ± 9.2[b]
BMI (kg/m^2)	27.8 ± 3.9	25.4 ± 3.4[a]	32.7 ± 4.6[a]	31.4 ± 4.7[a]	28.7 ± 4.6	26.5 ± 4.4[b]	28.6 ± 4.3	26.6 ± 4.4[b]
Total body fat mass kg)	27.8 ± 8.0	24.9 ± 7.3[a]	35.8 ± 9.3[a]	33.9 ± 8.6[a]	29.3 ± 8.8	26.4 ± 8.4[b]	29.6 ± 9.1	27.6 ± 8.0
Appendicular lean mass	25.8 ± 5.4	23.1 ± 5.1[a]	24.3 ± 4.7[a]	22.2 ± 4.8[a]	25.7 ± 5.5	23.3 ± 5.1[b]	24.7 ± 4.5	21.5 ± 4.5[a]
Physical activity (steps/day)	9159 ± 3301	8861 ± 3271	7029 ± 3156[a]	6872 ± 3070[a]	8949 ± 3404	8769 ± 3295	7974 ± 3147[b]	7476 ± 3244[b]
Current smoker (%)*	234 (50%)	182 (50%)	55 (51%)	47 (55%)	233 (50%)	188 (53%)	56 (50%)	41 (41%)
Number of chronic conditions	1.03 ± 1.09	1.00 ± 1.06	1.43 ± 1.31[a]	1.51 ± 1.28[a]	1.04 ± 1.10	1.03 ± 1.10	1.40 ± 1.27[b]	1.21 ± 1.20
25-hydroxyvitamin D	54.8 ± 17.2	52.2 ± 16.6	46.8 ± 16.2[a]	47.6 ± 14.4[a]	53.3 ± 17.5	51.5 ± 16.3	53.3 ± 16.4	50.5 ± 16.0
Falls risk Z-score	0.08 ± 0.82	0.23 ± 0.81	0.20 ± 0.74	0.28 ± 0.90	0.03 ± 0.76	0.15 ± 0.75	0.40 ± 0.94[b]	0.56 ± 0.98[b]

±Standard deviation; all tests are one-way ANOVA except * (Chi-square test)
[a] Significant difference to non-sarcopenic non-osteopenic
[b] Significant difference to non-dynapenic non-osteopenic

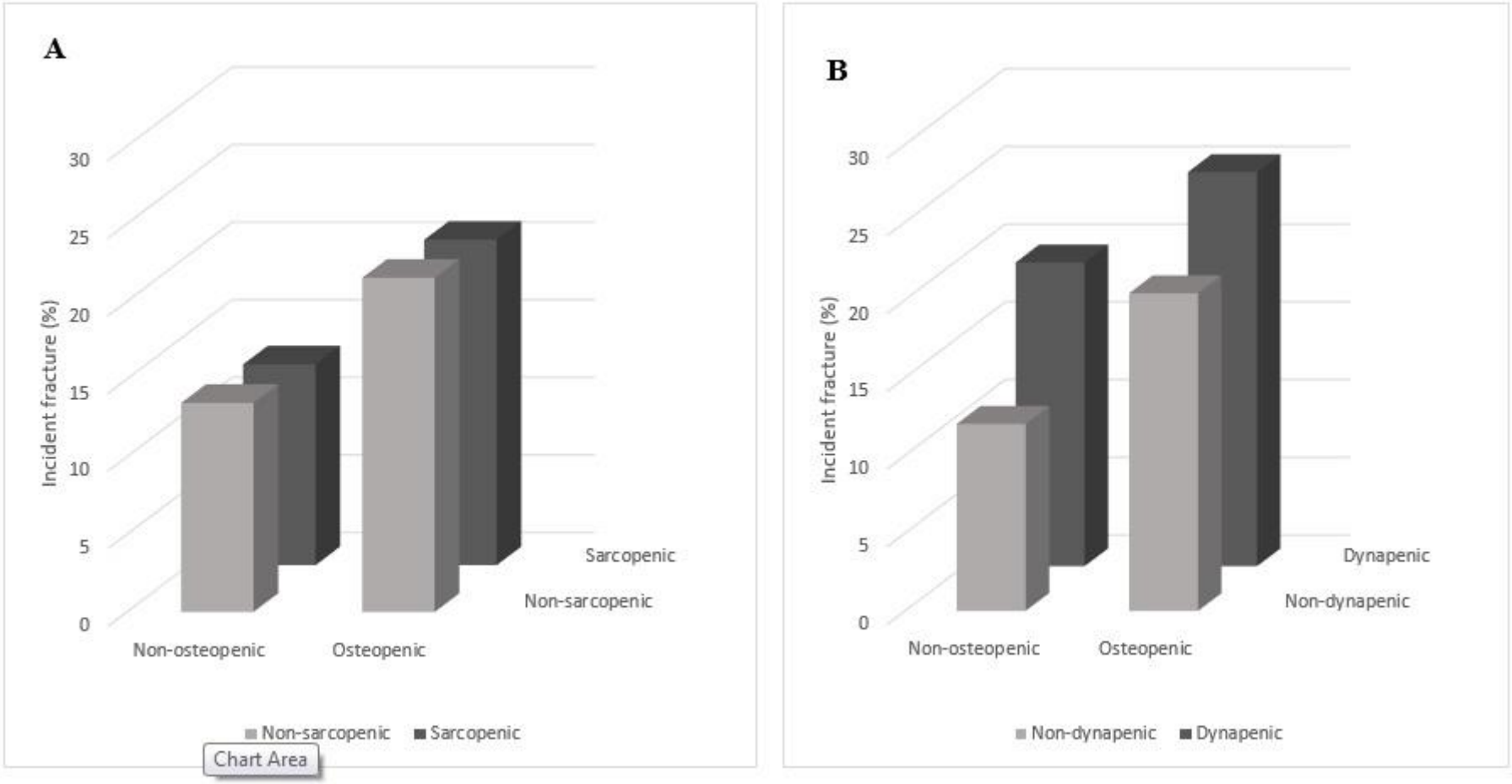

Figure 8.1: Incident fracture over 10 years stratified according to sarcopenic/osteopenic (A) and dynapenic/osteopenic (B) status.

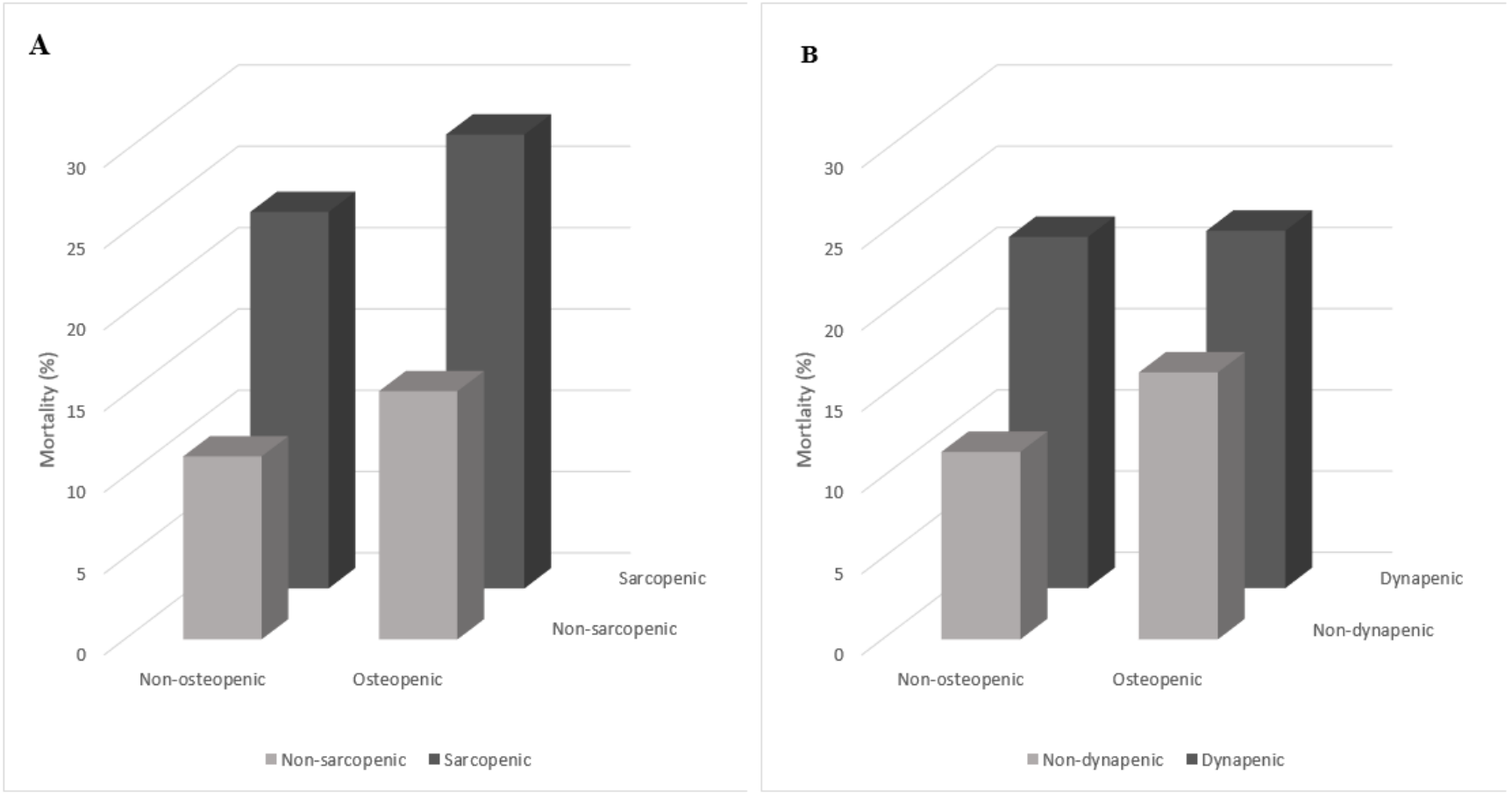

Figure 8.2: Mortality over 10 years stratified according to sarcopenic/osteopenic (A) and dynapenic/osteopenic (B) status.

Table 8.2: Relative risk (95% CI) for self-reported fracture over 10 years according to sarcopenic, dynapenic, and osteopenic categories.

	Non-sarcopenic, Non-osteopenic *N = 401*	Osteopenic non-sarcopenic *N =288*	Sarcopenic non-osteopenic *N =85*	Osteosarcopenic *N =62*
Unadjusted	REF	**1.60 (1.15, 2.23)**	0.96 (0.52, 1.76)	1.56 (0.90, 2.68)
Adjusted‡	REF	**1.50 (1.07, 2.10)**	0.97 (0.52, 1.81)	1.48 (0.83, 2.64)

	Non-dynapenic, Non-osteopenic *N = 399*	Osteopenic non-dynapenic *N =279*	Dynapenic non-osteopenic *N =87*	Osteodynapenic *N =71*
Unadjusted	REF	**1.70 (1.19, 2.42)**	1.62 (0.98, 2.68)	**2.11 (1.30, 3.40)**
Adjusted‡	REF	**1.63 (1.15, 2.31)**	**1.74 (1.05, 2.87)**	**2.07 (1.26, 3.39)**

Relative risk represents the increased risk compared to the REF (reference) group.

‡Adjusted for age, sex, physical activity (steps/day) and 25-hydroxyvitamin-D.
Bold text indicates significant at $P < 0.05$

Table 8.3: Relative risk (95% CI) for self-reported fracture over 10 years (muscle mass, strength and hip BMD as continuous variables)

Appendicular lean mass normalised to BMI (ALM/BMI)		
	ALM/BMI (/ 1 SD increase)	BMD (/1 SD decrease)
Univariable model	**0.78 (0.66, 0.92)**	**1.43 (1.21, 1.68)**
Multivariable model ‡	0.96 (0.73, 1.27)	**1.32 (1.09, 1.61)**
Handgrip strength (HGS)		
	HGS (/ 1 SD increase)	BMD (/1 SD decrease)
Univariable model	**0.72 (0.61, 0.86)**	**1.43 (1.21, 1.68)**
Multivariable model †	0.81 (0.63, 1.03)	**1.31 (1.08, 1.58)**

Relative risk represents an increase in 1 SD of ALM/BMI, HGS and 1 SD decrease in hip BMD.

‡Both ALM/BMI and hip BMD in the model with further adjustment for age, sex, physical activity (steps/day) and 25-hydroxyvitamin-D.

†Both handgrip strength and hip BMD in the model with further adjustment for age, sex, physical activity (steps/day) and 25-hydroxyvitamin-D.

Bold text indicates significant at $P < 0.05$

Table 8.4: Relative risk (95% CI) for mortality over 10 years according to sarcopenic, dynapenic, and osteopenic categories.

	Non-sarcopenic, Non-osteopenic *N = 471*	Osteopenic non-sarcopenic *N =367*	Sarcopenic non-osteopenic *N =108*	Osteosarcopenic *N =86*
Unadjusted	REF	1.36 (0.96, 1.92)	**2.06 (1.34, 3.15)**	**2.48 (1.62, 3.79)**
Adjusted‡	REF	1.27 (0.92, 1.76)	1.30 (0.88, 1.91)	**1.49 (1.01, 2.21)**

	Non-dynapenic, Non-osteopenic *N = 468*	Osteopenic non-dynapenic *N =353*	Dynapenic non-osteopenic *N =111*	Osteodynapenic *N =100*
Unadjusted	REF	**1.42 (1.01, 2.01)**	**1.87 (1.21, 2.89)**	**1.91 (1.22, 2.98)**
Adjusted‡	REF	1.27 (0.93, 1.72)	0.91 (0.62, 1.34)	1.03 (0.68, 1.57)

Relative risk represents the increased risk compared to the REF (reference) group.

‡Adjusted for age, sex, physical activity (steps/day) and number of chronic conditions.
Bold text indicates significant at $P < 0.05$

Table 8.5: Relative risk (95% CI) for mortality over 10 years (muscle mass, strength and hip BMD as continuous variables)

Appendicular lean mass normalised to BMI (ALM/BMI)		
	ALM/BMI (/ 1 SD increase)	BMD (/1 SD decrease)
Univariable model	1.12 (0.97, 1.28)	1.14 (0.97, 1.35)
Multivariable model ‡	1.01 (0.79, 1.28)	1.15 (0.98, 1.36)
Handgrip strength		
	HGS (/ 1 SD increase)	BMD (/1 SD decrease)
Univariable model	0.94 (0.82, 1.07)	1.14 (0.97, 1.35)
Multivariable model †	1.00 (0.83, 1.21)	1.16 (0.98, 1.36)

Relative risk represents an increase in 1 SD of ALM/BMI, HGS and 1 SD decrease in hip BMD.

‡Both ALM/BMI and hip BMD in the model with further adjustment for age, sex, physical activity (steps/day) and number of chronic conditions.

†Both handgrip strength and hip BMD in the model with further adjustment for age, sex, physical activity (steps/day) and number of chronic conditions.

Bold text indicates significant at $P < 0.05$

8.9 Discussion

This long-term prospective study investigates the association of sarcopenia and dynapenia in the presence of osteopenia with fracture and mortality over 10 years in a large sample of community-dwelling older adults. Incident fracture over 10 years was significantly higher among older adults who were osteodynapenic, dynapenic alone and osteopenic alone compared to those without dynapenia or osteopenia. Furthermore, mortality over 10 years was significantly higher in participants with osteosarcopenia compared to those without sarcopenia or osteopenia. Notably, the combination of osteopenia with sarcopenia or dynapenia did not lead to a significantly greater mortality or fracture risk compared to having these conditions on their own. These findings suggest that the combined effect of osteopenia and sarcopenia or dynapenia on fracture and mortality risk, respectively, may not be greater than that of each individual condition.

The coexistence of low BMD and low muscle strength (osteodynapenia), but not low BMD and low muscle mass (osteosarcopenia), significantly increased the risk of fracture over 10 years. Low BMD is an established risk factor for fracture [282, 283] and muscle strength exerts significant force on the bone, contributing to the maintenance of bone strength [284]. Hence, both low muscle strength and low BMD in older adults may not adequately stimulate osteogenesis thereby increasing fracture risk in the event of a fall. Furthermore, prior studies have suggested that low muscle strength (but not muscle mass) significantly increases falls risk in older people, potentially due to accelerated age-related decline in muscle strength compared to muscle mass [61, 201]. This may explain why the coexistence of low BMD and low muscle strength appears to impact more on fracture risk than low muscle mass. It has been suggested that the combined assessment of low muscle and bone mass may improve

fracture risk assessment compared to low muscle or low BMD alone [285]. We found that, although fracture risk was higher in older adults with osteodynapenia compared to those with neither condition, the risk of fracture was not significantly greater compared to having osteopenia or dynapenia alone. This finding is consistent with previous studies which suggest that combining low muscle and bone mass assessment may not improve prediction of fracture risk in individuals with either condition [286].The fact that the risk of fracture with osteodynapenia was not significantly greater compared to having osteopenia or dynapenia alone suggests that combining these assessments may not improve prediction of fracture risk. When BMD, muscle mass and strength were considered as continuous variables, increasing BMD but not muscle mass or strength was associated with a lower risk of fracture. There have been several attempts to identify HGS thresholds for the identification of clinically relevant weakness [135, 136]. The lowest 20% of the sex-specific distribution of HGS, as used in this study, has been shown to be predictive of fracture and poorer health outcomes in older people [63, 201].

The coexistence of low BMD and low muscle mass (osteosarcopenia), but not low BMD and low muscle strength (osteodynapenia), significantly increased the risk of mortality over 10 years. While osteosarcopenia was associated with increased mortality risk, the risk was not significantly greater compared to having osteopenia or sarcopenia alone. Contrary to the risk of fracture it was muscle mass (not strength) that was important for mortality. Low ALM/BMI is indicative of high body fat percentage which has been shown to be associated with mortality risk [287]. A prior study also showed that low BMD is predictive of mortality over 6 years, independent of comorbidities, physical activity and previous history of fractures [288]. Therefore, it is plausible that older adults with both low BMD and low ALM/BMI had an additional risk of mortality compared to individuals with neither condition. Low muscle

mass (as opposed to low strength) combined with low BMD may increase mortality risk because muscle mass serves as a reliable protein reserve and plays a key role in recovery from illness or trauma, including fracture healing [289]. Indeed, survival following fracture is lower in older adults with low muscle mass compared to those with normal muscle mass [169]. For instance, in a sample of 192 older adults admitted to the hospital following acetabular fracture, mortality over one year was 28.6% in those with low muscle mass compared with 12.3% in those with normal muscle mass [169]. Interestingly, no significant relationships were observed bewteen muscle strength or mass and BMD as continuous variables, and mortality after adjusting for covariates. This finding is consistent with prior studies providing evidence for a non-linear relationship between muscle mass, BMD and mortality [25, 288].

The strength of this study includes the 10-year follow-up period and the use of a population-based sample which increases its generalizability. In addition, body composition was assessed using DXA, a gold standard for diagnosing osteopenia/osteoporosis and a valid instrument for measuring muscle mass. However, this study has a number of limitations. Firstly, there was 19% missing data for incident fracture due to loss to follow-up. Such missing data is not unexpected in a long-term prospective study involving older people. However, the results of sensitivity analysis for missing data using inverse probability weighting were similar to the complete case analyses (Table 8.6 and Table 8.7). Secondly, incidence of fracture was self-reported and may be subject to recall bias. However, inaccuracy of fracture recall is unlikely as fractures are a major life event [232]. Thirdly, we were unable to perform cause-specific analysis for mortality as data on the specific cause of death was not available for all the participants. Lastly, established definitions for sarcopenia were not used in this study as only 4 participants (men=4; women=0) were classified has having sarcopenia according to the

established cut-points for ALM/BMI by the Foundation for National Institute of Health (FNIH) sarcopenia project. In contrast we defined cut-points in the lowest 20% of the sex-specific distribution of muscle mass and strength, which has previously been used as a diagnostic measure for sarcopenia (8, 12). Despite this we were able to find important associations using this diagnostic measure for low muscle mass and strength.

In conclusion, low BMD combined with low muscle mass or strength does not significantly increase the risk of fracture or mortality compared to having low BMD or low muscle mass/strength alone, suggesting that combined assessments may not add additional risk for fracture and mortality.

Table 8.6: Relative risk (95% CI) for self-reported fracture over 10 years according to sarcopenic, dynapenic and osteopenic categories. (Inverse probability weighting)

	Non-sarcopenic, Non-osteopenic *N = 401*	Osteopenic non-sarcopenic *N =288*	Sarcopenic non-osteopenic *N =85*	Osteosarcopenic *N =62*
Unadjusted	REF	**1.68 (1.19, 2.38)**	1.01 (0.54, 1.90)	**1.85 (1.07, 3.21)**
Adjusted‡	REF	**1.59 (1.11, 2.27)**	0.99 (0.51, 1.92)	1.73 (0.95, 3.14)

	Non-dynapenic, Non-osteopenic *N = 399*	Osteopenic non-dynapenic *N =279*	Dynapenic non-osteopenic *N =87*	Osteodynapenic *N =71*
Unadjusted	REF	**1.80 (1.25, 2.60)**	1.57 (0.93, 2.64)	**2.09 (1.26, 3.46)**
Adjusted‡	REF	**1.72 (1.19, 2.49)**	**1.60 (0.95, 2.71)**	**2.02 (1.19, 3.44)**

Relative risk represents the increased risk compared to the REF (reference) group.

‡Adjusted for age, sex, physical activity (steps/day) and 25-hydroxyvitamin-D.
Bold text indicates significant at $P < 0.05$

Table 8.7: Relative risk (95% CI) for self-reported fracture over 10 years (muscle mass, strength and hip BMD as continuous variables) (Inverse probability weighting)

Appendicular lean mass normalised to BMI (ALM/BMI)

	ALM/BMI (/ 1 SD increase)	BMD (/1 SD decrease)
Univariable model	**0.80 (0.67, 0.95)**	**1.48 (1.24, 1.76)**
Multivariable model ‡	1.00 (0.75, 1.33)	**1.37 (1.12, 1.68)**

Handgrip strength (HGS)

	HGS (/ 1 SD increase)	BMD (/1 SD decrease)
Univariable model	**0.75 (0.63, 0.91)**	**1.48 (1.24, 1.76)**
Multivariable model †	0.88 (0.68, 1.15)	**1.37 (1.11, 1.67)**

Relative risk represents an increase in 1 SD of ALM/BMI, HGS and 1 SD decrease in hip BMD.

‡Both ALM/BMI and hip BMD in the model with further adjustment for age, sex, physical activity (steps/day) and 25-hydroxyvitamin-D.

†Both handgrip strength and hip BMD in the model with further adjustment for age, sex, physical activity (steps/day) and 25-hydroxyvitamin-D.

Bold text indicates significant at $P < 0.05$

Chapter 9: Summary and Future Directions

9.1 Prelude

Age-related decline in skeletal muscle mass and strength is a major public health problem that is associated with functional decline and loss of independence in older people. With the ageing population in Australia, the absolute number of older people is expected to increase, contributing to substantial increase in direct and indirect costs attributed to age-related muscle loss and its sequelae. Prior studies suggest that modifiable lifestyle factors such as physical activity may be related to muscle loss. However, limited long-term prospective studies have examined these associations. Longer term prospective studies are crucial in the design of long-term interventions to reduce age-related muscle loss and its associated health consequences. This thesis examined the risk factors for age-related muscle loss over a decade and the impact that muscle loss has on important clinical outcomes like falls risk, fracture, HRQoL and mortality.

9.2 Summary of findings

Chapter 4 describes the first longitudinal study to examine the associations of within-person variability in physical activity, 25(OH)D, knee pain and dysfunction with muscle loss over a long-term, in addition to traditional between-person comparisons. Participants with a higher physical activity and 25(OH)D, on average, had a higher lower-limb muscle mass, strength and muscle quality. Furthermore, participants with a higher WOMAC global score, on average, had significantly lower muscle strength, muscle quality but not muscle mass. Interestingly, at time-points when an individual had a higher physical activity, 25(OH)D and lower WOMAC global score than their

average level, they also had a higher muscle strength and muscle quality. Generally, within-person estimates were smaller in magnitude compared to the between-person estimates potentially because error variance is reduced when individual are compared to themselves. This study builds on our knowledge from the between-person analysis, as it demonstrates that within-person variability in physical activity, 25(OH)D, knee pain and dysfunction have independent effects on the muscle. Chapter 6 uses a similar analysis method to examine the associations of between-person and within-person variability in physical activity, 25(OH)D, knee pain and dysfunction with falls risk. A novel finding of this study was that falls risk score was lower at time-point when an individual had a lower WOMAC global score and a higher MVPA above their average level. Between-person but not within-person increases in 25(OH)D was associated with a lower falls risk score. The within-person findings presented in Chapter 4 and 6 may be an incentive to further promote physical activity in otherwise inactive older people.

Chapter 5 compares the performance of low muscle mass and function with falls risk, incident fracture and mortality over 10 years. Discrepancy exists in the rate of decline in muscle mass and strength and age-related muscle loss is higher in lower-limbs compared to upper-limb. Identifying the most valid predictor of important health outcomes is vital for developing interventions to prevent older people at risk. Baseline low muscle strength (LMS and HGS) and muscle quality (LMQ and UMQ) but not the various indices of muscle mass (ALM/HH, ALM/BMI, ALMW and ALMR) were associated with a higher falls risk at 10 years. Low handgrip strength and low ALM/BMI were the only significant predictors of fracture and mortality respectively. Chapter 8 examined whether the prognostic ability of HGS and ALM/BMI as the only

predictor of fracture and mortality respectively, would be greater when combined with osteopenia. Indeed, mortality risk was significantly higher in participants with both osteopenia and low ALM/BMI compared to those without low ALM/BMI or osteopenia. Similarly, incident fracture was significantly higher in participants with both low HGS and osteopenia, compared to those without osteopenia or low HGS. However, osteopenia combined with low ALM/BMI or HGS does not significantly increase the risk of fracture or mortality compared to having osteopenia or low HGS / low ALM/BMI alone, suggesting that combined assessments may not add additional risk for fracture and mortality.

Chapter 5 showed that low muscle strength (HGS and LMS) but not muscle mass were associated with lower falls risk and that low muscle mass, particularly ALM/BMI was the only predictor of mortality in this cohort of older people. Chapter 7 assessed whether ALM/BMI, LMS and HGS had a different impact on HRQoL over 10 years. Participants (both men and women) with low LMS at baseline had a clinically meaningful difference in HRQoL over 10 years compared to those with normal strength. Sex modified the association between low HGS at baseline and HRQoL over 10 years such that women with low baseline HGS had a clinically meaning lower HRQoL over 10 years whereas no significant relationship was observed in men. There was a weaker but statistically significant association between low ALM/BMI at baseline and HRQoL over 10 years.

In conclusion, the prospective study of community-dwelling older people presented in this thesis demonstrates that, in addition to traditional between-person associations, variability in physical activity, 25(OH)D, knee pain and dysfunction within an

individual over time relate to muscle changes and falls risk. Furthermore, muscle strength, which can be easily measured in clinical practice, appears more important than muscle mass for identifying individuals with a higher falls risk, fractures and poorer quality of life. However, muscle mass appears to be a better predictor of mortality risk. The predictive ability of low HGS and low ALM/BMI in identifying individuals with a higher fracture and mortality risk respectively, was stronger when these measures were combined with low BMD. Recommendations for further research is provided in the following section.

9.3 Future directions

Findings from the prospective population-based studies presented in this thesis have provided novel and additional information on the long-term risk factors for age-related muscle loss and the impact that this muscle loss has on multiple health outcomes over a decade in community-dwelling older adults. These findings offer a new pathway for public health efforts and interventions aimed at minimising muscle loss and its sequel.

For instance, the observation that within-person increase in physical activity was associated with higher muscle mass and function and a lower falls risk score could be relevant in personalised public health messages aimed at reducing muscle loss and falls risk in community-dwelling older people. This could be achieved by highlighting that, although maintaining a consistently higher physical activity is beneficial for muscle and lower falls risk (between-person effects), increases in physical activity (irrespective of the current level of physical activity) also has benefits on muscle

mass, strength and muscle quality and also helps reduce falls risk (within-person effects).

The health benefit of physical activity highlighted in Chapter 4 and 6 of this thesis has been documented in prior studies [68, 71]. Yet, only 25 – 55% of older people in Australia meet or exceed the recommended physical activity guidelines [290]. Multimodal interventions including lifestyle counselling and personalised physical activity goals can increase physical activity participation at 12 months [291]. However, the benefit of such interventions beyond 12 months is unclear [291]. Future studies investigating interventions to promote physical activity participation over the long-term is critical to preventing muscle loss and poor musculoskeletal health outcomes in the older people. Such interventions may include cognitive-behavioural therapy that empowers older people to adopt a behaviour that would help sustain physical activity participation over long-term.

Chapter 5 highlighted that low HGS was a consistent predictor of falls risk and fracture over a decade. This finding is consistent with studies showing that low HGS is associated with important clinical health outcomes, with studies suggesting HGS as a vital assessment tool in clinical settings [292]. Despite the available epidemiological data showing the relevance of handgrip strength as a non-invasive, cheap and readily available tool in identifying individuals with poor health outcome, studies demonstrating the feasibility of translating handgrip strength assessments in clinical settings are limited. Such studies are vital in implementing handgrip strength assessment in routine clinical practice. Recently, Ibrahim et al published the protocol of the Grip Strength Routine Implementation (GRImP) study which was aimed at

evaluating the acceptability and feasibility of HGS assessment in acute medical wards of an hospital in the UK [293]. While the completion of this study may provide crucial information on translating HGS assessments into routine clinical practice on acute medical wards, studies evaluating the feasibility of HGS assessments in other clinical settings including outpatients and rehabilitation wards are warranted. There is a wide heterogeneity in the protocol used for the assessments of HGS [294]. Therefore, for HGS assessments to be relevant in clinical settings, its measurements need to be standardised for comparisons and follow-up of patients in different health settings [295]. For instance, several factors including posture, the position of the elbow and the wrist during the assessments of HGS may influence the value of the grip strength [294]. Hence, variations in the protocols used for the assessments of HGS may result in the misclassification of different individuals as having low HGS [294].

Chapter 6 highlight the significance of the relationship of dynamic within-person variability in physical activity, serum 25(OH)D, knee pain and dysfunction with physiological falls risk. Whilst the PPA is an objective falls risk measure that is not subjected to recall bias, this measure assessed physiological falls risk that may not necessarily translate to actual falls. Further studies need to confirm the relationship of dynamic within-person variability in physical activity, serum 25(OH)D, knee pain and dysfunction using actual falls data as an outcome.

Furthermore, it is possible that within-person variability in the risks for falls follow a specific trajectory for different groups of older people. Future studies could adopt a group-based trajectory modelling approach to characterise older adults into similar

falls trajectories and examine the risk factors for each trajectory. Findings from such studies are crucial to help better select which patients would most benefit from a falls prevention intervention. Older people are heterogenous, hence, falls prevention interventions targeting older people with similar falls trajectory could be more effective.

The interconnection among the multiple risk factors for falls risk and muscle loss examined in this thesis are likely to be complex and should be studied in detail in future studies. For instance, serum 25(OH)D, knee pain and dysfunction could be a possible pathway through which physical activity affects falls risk, muscle mass and function. It is also possible that physical activity mediates the association between the knee pain/dysfunction and loss of muscle mass and function. Hence, the complex mediation pathways among these variables could be studied using multivariate analysis technique like structural equation modelling.

Lastly, the novel within-person analysis method used in this thesis could be used to examine between-person and within-person differences for other musculoskeletal outcomes (for example osteoarthritis) or for other populations (for instance, BMD loss in younger age groups).

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